VOLUME 67 *January, 1953* NUMBER 1

THE AMERICAN REVIEW OF TUBERCULOSIS

OFFICIAL JOURNAL OF AMERICAN TRUDEAU SOCIETY
MEDICAL SECTION OF NATIONAL TUBERCULOSIS ASSOCIATION

CONTENTS

Extrapleural Pneumothorax. JOHN W. STRIEDER AND EDWARD A. GAENSLER... 3
Intermediary Report of 102 Streptomycin-Protected Pulmonary Resections. JAMES D. MURPHY AND BARNEY B. BECKER... 22
Bronchiectasis: A Comparative Study. JOSEPH GORDON AND PHILIP C. PRATT.. 29
Transient Undiagnosed Intrathoracic Lymphadenopathy in Apparently Healthy Persons. AARON D. CHAVES AND HANS ABELES... 45
The Cytology of the Tubercle Bacillus with Reference to Mitochondria and Nuclei. LOREN C. WINTERSCHEID AND STUART MUDD... 59
Tuberculosis Control in Hospital Personnel. A Review. H. MCLEOD RIGGINS... 74
Tuberculosis Among Jews. Mortality and Morbidity Among Different Jewish Ethnic Groups. Tuberculosis Among Yemenite Jews. Etiologic Factors. JOSEPH RAKOWER... 85
Horner's Syndrome Complicating Surgery for Pulmonary Tuberculosis. A Review of Five Cases. EDWARD J. WELCH... 94
Notes:
Effect of a Minimal Dose of Cortisone Combined with a Subeffective Dose of Dihydrostreptomycin on Experimental Guinea Pig Tuberculosis. NORMAN MOLOMUT AND DAVID M. SPAIN... 101
A Note on the pH of Tuberculous Empyema. IRVING N. WOLFSON AND RICHARD J. FEINBERG... 103
Incidence of Bacterial Resistance Encountered with Tuberculosis Chemotherapy Regimens Employing Isoniazid Alone and in Combination with Intermittent Streptomycin. WILLIAM E. DYE, HELEN P. LYNCH, AND ATLANTA G. BREES... 106
Control Study of Comparative Efficacy of Isoniazid, Streptomycin-Isoniazid, and Streptomycin—Para-Aminosalicylic Acid in Pulmonary Tuberculosis Therapy: II. Report on Twenty-Week Observations on 390 Patients with Streptomycin-Susceptible Infections. FRANK W. MOUNT AND SHIRLEY H. FEREBEE... 108
American Trudeau Society:
Award of the Trudeau Medal for 1952... 114
Notes... 120
Necrology... 122
Abstracts... 1

Published Monthly at Mount Royal and Guilford Avenues, Baltimore 2, Maryland by the National Tuberculosis Association • Business Off., 1790 Broadway, New York 19, N.Y.

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Medical Section of National Tuberculosis Association

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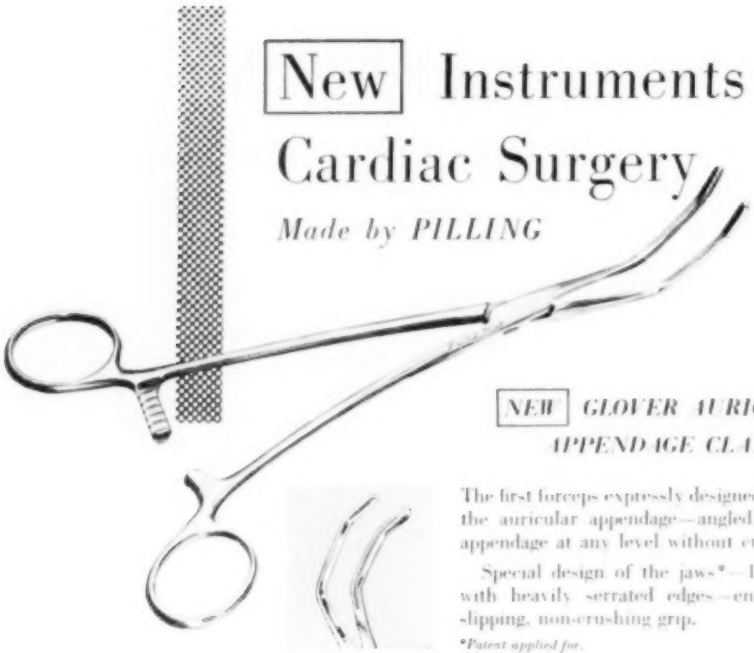

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THE AMERICAN REVIEW
OF
TUBERCULOSIS

VOLUME 67 | *January, 1953* | NUMBER 1

EXTRAPLEURAL PNEUMOTHORAX[1, 2, 3]

JOHN W. STRIEDER AND EDWARD A. GAENSLER

(Received for publication May 28, 1952)

INTRODUCTION

The current difficulty in evaluating extrapleural pneumonolysis is not due to a paucity in the number of operations reported. Only four years after the enthusiastic introduction of the modern operation in 1936 (1, 2), Dolley, Jones, and Skillen reviewed 36 papers dealing with the results of the procedure in 2,277 patients (3). Many advances in antimicrobial therapy, transfusion technique, cardiorespiratory studies, anesthesia, enzymatic fibrinolytic therapy, and laminagraphy have been made since that time, and the procedure should be re-evaluated in the light of these developments.

In some clinics, extrapleural pneumothorax was employed cautiously at first but, because of encouraging results, the indications were later widened. Large series of cases were collected and the results, in general, appeared to have been good (4–8). Although these results have been published within the past five years, the operations were performed during an earlier period. Others reserved the procedure for their worst-risk patients. This attitude may account for some of the poor results reported and for their ultimate dissatisfaction with the operation (9–11). A few long-term follow-up studies are available which deal with the results of the operation used with the broadest indications (12, 13). As has always been the situation, the outcome varied with the extent of the disease. The long-term outcome was satisfactory and it was apparently believed that the results more than justified the additional effort required for the proper management of these patients.

[1] From the Thoracic Surgery Service, Sanatorium Division of the Boston City Hospital, Mattapan, and the Department of Surgery, Boston University School of Medicine; and the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

[2] Presented before the Medical Session, as part of the *Surgical Session on Tuberculosis*, at the 48th annual meeting of the National Tuberculosis Association, Boston, Massachusetts, May 28, 1952.

[3] This study was supported (in part) by research grants from the Foundation for the Study and Treatment of Thoracic and Related Diseases; from the Committee on Medical Research of the American Trudeau Society, medical section of the National Tuberculosis Association; and from the Division of Research Grants and Fellowships of the National Institutes of Health, Public Health Service.

The very advances which have made a re-evaluation of extrapleural pneumothorax desirable have also been responsible for the wider choice of operative procedures now available for the treatment of pulmonary tuberculosis. In 1936, if artificial pneumothorax proved ineffectual, the only practical alternative to thoracoplasty was extrapleural pneumonolysis. Today this operation must compete, not only with several variations of less formidable and more satisfactory thoracoplasty, but also, under certain circumstances, with various types of pulmonary resection. Lucite sphere plombage was also introduced during this period as a means of filling the extrapleural space in patients who presented previously well-recognized indications for extrapleural pneumonolysis. It was hoped that this technique would also be preferable to thoracoplasty in many cases requiring collapse therapy (14), but the number of complications and the early end results may not justify its continued use (15, 16). Although other promising filling materials have recently been introduced (17), plombage with plastic substances is at present reserved for the subcostal-extraperiosteal space in most clinics. In addition to a renewed appraisal of extrapleural pneumonolysis, a clarification of its current place in the therapeutic armamentarium seems indicated.

Indications

At the Sanatorium Division of the Boston City Hospital at Mattapan, extrapleural pneumothorax has been integrated in the surgical program on the following premises:

(*1*) The procedure is not desirable as a permanent collapse measure because of the danger of losing the space, the danger of late infection, and the need for frequent refills. The cosmetic advantages of the operation are outweighed by these drawbacks.

(*2*) Subpleural or peripheral cavitation is an absolute contraindication.

(*3*) Extrapleural pneumothorax is more sparing of pulmonary function than any other form of active collapse therapy except perhaps pneumoperitoneum.

From these three principles two indications for the operation have evolved:

Group I. Far advanced bilateral tuberculosis: Patients in this category were of three types:

(*a*) Those with a pulmonary reserve too low for other types of collapse or resection. In these circumstances, pulmonary insufficiency was always due to previous contralateral collapse or resection.

(*b*) Those with far advanced bilateral disease with contralateral cavitation which might require contralateral surgery in the near future.

(*c*) Those with far advanced disease causing active hemorrhage which required emergency treatment in spite of pulmonary insufficiency. This condition was invariably associated with either one or both of the first two situations.

Group II. Extrapleural pneumothorax as a first stage to a modified thoracoplasty: Patients were selected for this procedure if they had only moderately advanced disease with cavitation particularly favorable for collapse therapy and if a good cosmetic result was of unusual importance.

OBSERVATIONS

The indications listed above were rigidly adhered to, and the result was a relatively infrequent use of the procedure. Of 323 new patients admitted to the Thoracic Surgery Service during the four-year period between November, 1947,

and November, 1951, more than one-half were subjected to standard staged thoracoplasty or subcostal plombage. Extrapleural pneumonolysis was elected as the procedure of choice in only 14 per cent of all cases (figure 1). During the first two years standard thoracoplasty was the most frequent primary procedure, but during the last two years subcostal plombage and resection were used more often.

The patients included in this series were selected to allow for a minimum follow-up period of one year. During this time, 47 extrapleural operations and 140 standard thoracoplasties were performed. It was possible, in retrospect, to compare the two groups as far as extent of disease, severity of symptoms, and pulmonary function were concerned (figure 2). The patients with extrapleural pneumothorax were divided into two groups as outlined above. It is apparent

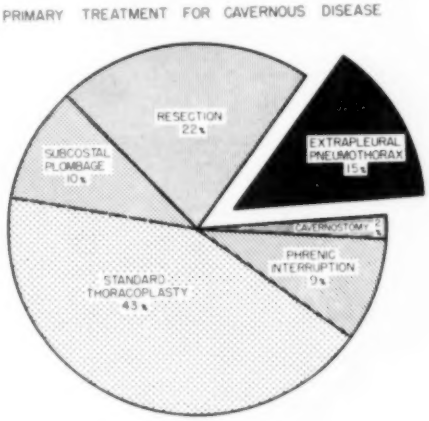

FIG. 1. Primary surgical procedures selected for treatment of cavernous pulmonary tuberculosis. Procedures employed for the treatment of empyema and operations performed when other previous surgical treatment on the same side had failed are not included.

that those in *Group I* had more extensive disease than the patients subjected to standard thoracoplasty, since all of the former were classified as far advanced. The patients in *Group II* had less extensive disease than the thoracoplasty patients. The majority had only moderately advanced disease. The same applies to severity of symptoms. Most of the patients in *Group I* were severely ill, while most of those in *Group II* had no or only slight symptoms. The most striking comparison could be made on the basis of preoperative pulmonary function classified as good, fair, or poor. In *Group I* only 35 per cent had good function and in one-half the function was considered poor. There were no patients with marked pulmonary insufficiency in *Group II*. Again, the patients subjected to standard thoracoplasty fell between these two extremes.

Roentgenograms are shown to illustrate typical indications. In the first pa-

tient (figure 3), pneumonolysis was elected because of pulmonary insufficiency due to previous contralateral collapse therapy and bronchial asthma. The operation was carried out on the right side after intrapleural pneumothorax of many years' duration had proved ineffective. Previously, open drainage had been performed for a giant cavity in the apical segment of the left lower lobe. Phrenic interruption and pneumoperitoneum had been added to increase the effectiveness of the drainage.

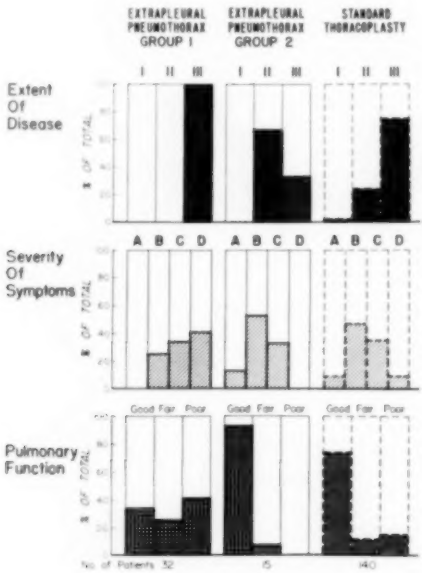

FIG. 2. Extent of disease, severity of symptoms, and preoperative pulmonary function of 47 patients who had extrapleural pneumonolysis compared with 140 patients who had standard thoracoplasty during the same period. Patients in *Group I* were selected for the extrapleural operation because they had pulmonary insufficiency due to previous contralateral collapse or because they had bilateral cavernous disease. The operation was done in *Group II* as a first stage to a modified parietoplasty in patients in whom a good cosmetic result was of unusual importance.

The extrapleural operation was chosen in the next patient (figure 4) because contralateral surgery was contemplated. After left extrapleural pneumonolysis, bed rest and pneumoperitoneum promoted healing of the lesion on the right, and the extrapleural space eventually was converted by a modified thoracoplasty.

Massive hemorrhage and pulmonary insufficiency due to intrapleural pneumothorax on the opposite side was the indication for pneumonolysis in the next patient (figure 5). One year later, when a residual cavity was observed under the extrapleural air space on the right (figure 5 *C*), the left lung was permitted to re-expand and the right lower lobe was resected while the extrapleural space was maintained (figure 5 *D*).

The incidence of these indications is summarized in table 1. In 68 per cent the operation was performed in the face of far advanced bilateral disease or previous contralateral collapse or resection. In 8 of 11 patients with contralateral cavern-

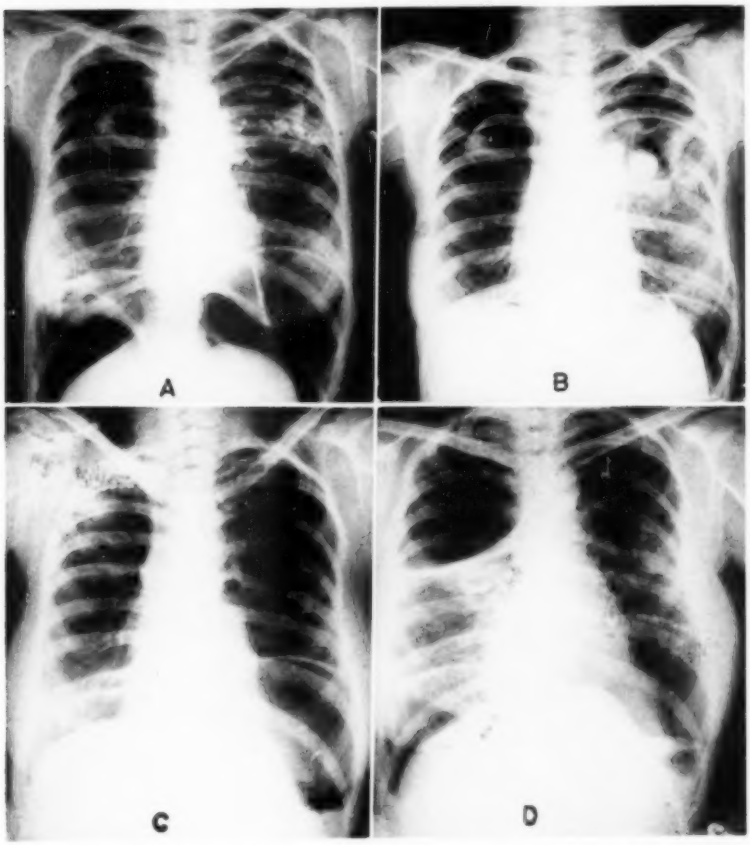

FIG. 3. Roentgenogram of the chest of a 32 year old woman with intrapleural therapeutic pneumothorax on the right and a giant cavity at the left hilus (*A*). The latter cavity was opened and drained (*B*). Pneumoperitoneum and a left phrenic crush were added to promote closure. Cavernostomy was successful and the ineffective right pneumothorax was abandoned. Extrapleural pneumonolysis was selected for closure of residual cavities on the right (*D*) because of severe pulmonary insufficiency due to previous disease and surgical therapy and because of complicating bronchial asthma.

ous disease, the cavities healed spontaneously during the ensuing period of bed rest. In the remaining 3, further contralateral surgery was necessary and extrapleural pneumonolysis was chosen in all 3 cases.

Operative Management

Before operation, all patients had thorough roentgenographic mapping of the areas of disease and all had bronchoscopic and pulmonary function studies, including bronchospirometry (18). Special emphasis was placed on preoperative postural drainage, and operations were performed by preference in the afternoon to allow additional time for mobilization of secretions.

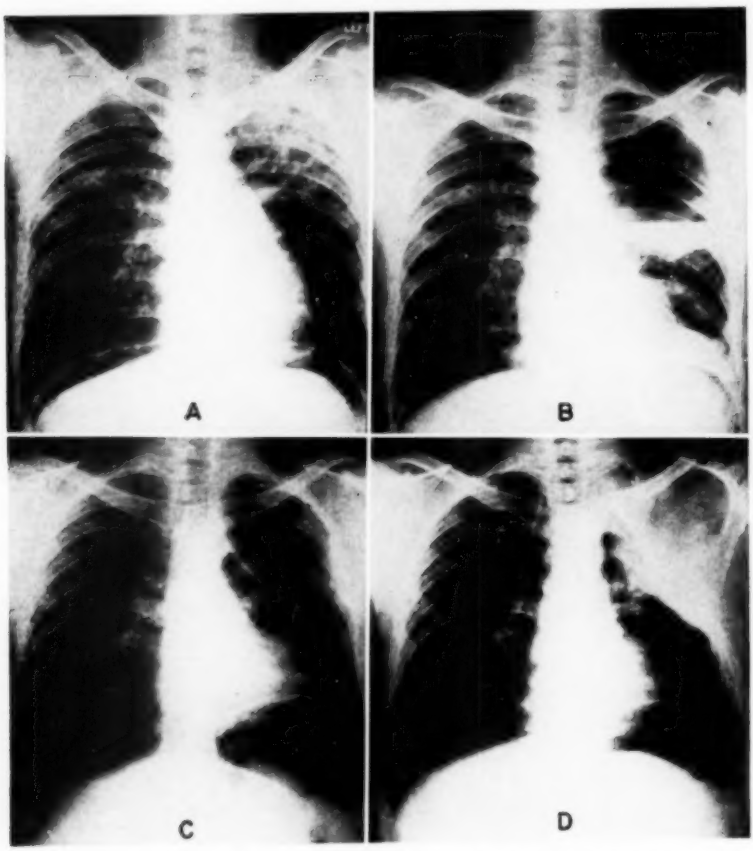

FIG. 4. Roentgenogram of the chest of a 42-year-old man showing extensive cavitation at the apex of the left lung (*A*). Extrapleural pneumothorax was selected because of infiltration and a small cavity in the mid-lung field on the other side (*B*). Postoperatively, the cavity in the right lung closed while on bed rest supplemented by pneumoperitoneum (*C*). The extrapleural pneumothorax was converted to a modified thoracoplasty (*D*). Deformity is minimized, possibly because the first rib and transverse processes were left intact.

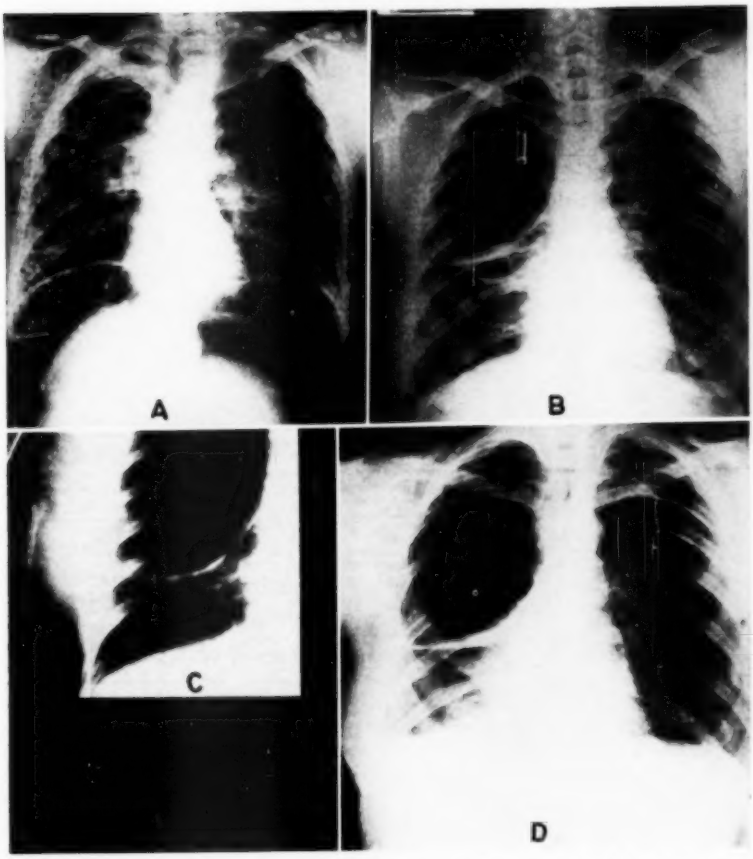

FIG. 5. Roentgenogram of the chest of a 38-year-old woman who had a re-expanded pneumothorax lung on the right with a large, thick-walled cavity at the hilus and multiple small cavities at the apex. An intrapleural pneumothorax on the left is still in force and a recent extension of disease on that side can be seen (*A*). Pneumoperitoneum, induced because of hemoptysis, was abandoned and an extrapleural operation was performed when bleeding became life-threatening. This operation was chosen because surgery was required in spite of severe pulmonary insufficiency and contralateral collapse therapy (*B*). No further bleeding occurred after operation but gastric washings were intermittently positive for tubercle bacilli one year later. Laminagraphy demonstrated a residual cavity at the apex of the lower lobe under the air space (*C*). The intrapleural pneumothorax on the opposite side was abandoned and the right lower lobe was resected without entering the extrapleural space (*D*). This patient has been well and at home for two years.

Endotracheal nitrous oxide-oxygen-ether anesthesia was usually employed, although in better-risk patients intravenous thiopental-curare was occasionally used.

A modified thoracoplasty incision was made. Extrapleural dissection was carried in all cases to the seventh rib posteriorly, the fifth rib laterally, beyond the third rib anteriorly, and along the mediastinum to the azygos vein on the right side and over the arch of the aorta on the left side. The lateral and posterior extent of the dissection was adapted to the extent of the disease. No difficulties were encountered in finding or pursuing the extrapleural plane, probably because patients with obvious subpleural cavitation were excluded. The wound was thoroughly washed with physiologic saline solution and 200 cc. of this solution containing 1 gm. of streptomycin and 200,000 units of penicillin were left in the developed space. All of the usual devices to achieve airtight closure in layers were employed. Immediately after operation the pressure in the extrapleural space was adjusted to neutral.

The early controversy concerning the advisability of tube drainage for more convenient aspiration of fluid and early refills (1, 2) was not settled. If the lung was hard, if it showed poor collapse, or if the disease was complicated by emphysema, a tube was used and

TABLE 1

INDICATIONS FOR EXTRAPLEURAL PNEUMONOLYSIS

INDICATIONS	NUMBER OF OPERATIONS	PER CENT OF TOTAL
Group I. Far advanced bilateral disease		
(a) Poor pulmonary reserve due to previous contralateral collapse or resection	17	36
(b) Contralateral cavity with likelihood of further surgery on the other side	11	23
(c) Active hemorrhage in the face of pulmonary insufficiency	4	9
Total, *Group I*	32	68
Group II. Moderately advanced disease with favorable prognosis, operation as first stage to modified thoracoplasty	15	32
Total, *Groups I* and *II*	47	100

probably aided in the management during the first few postoperative days. Usually the tube was omitted because it was believed that it might predispose to infection.

The postoperative care was time-consuming and more elaborate than that required after any other surgical procedure employed by the writers. A portable roentgenogram was obtained a few hours after the operation and twice daily thereafter for two or three days. Streptomycin, 1 gm., and penicillin, 500,000 units, were given intramuscularly every day for fourteen days and the same amounts of streptomycin and penicillin were injected in the extrapleural space daily for fourteen days. It was thought that postoperative infection of the extrapleural space would be minimized if it were kept dry. All fluid was therefore aspirated from the space in so far as possible and the space was usually dry within ten days. Every three hours after operation the patients were urged to cough regardless of complicating subcutaneous emphysema. Patients whose cough was feeble or ineffective had intratracheal catheter suction at regular intervals.

Air refills varied within wide limits in frequency, amounts, and final pressures. Air injections were governed by the pressure responses and by the appearance of the lung on portable roentgenograms. Often, collapsed portions of the lung showed atelectatic changes,

and relatively infrequent refills at low pressures were required. When the lung was covered with a thick cortex and showed no atelectatic changes, weekly refills with pressures up to 40 cm. of water were needed.

Extrapleural pneumothorax as a first stage to a modified thoracoplasty: This planned two-stage procedure, suggested by Harken and Cincotti (19), requires extrapleural pneumonolysis with dissection to the hilus as a first stage. When the sputum has been "converted" and the extrapleural lining has shown adequate thickening, the second, or modified thoracoplasty stage, is performed. The necessary number of ribs, as determined by the preoperative roentgenograms, are resected subperiosteally in the usual manner. The transverse processes and the first rib are left intact. The extrapleural space is then incised along the transverse processes posteriorly, upward along the inferior border of the first rib, and anteriorly along the stumps of the resected ribs until the base of the space has been reached. The flap created in this manner consists of tough extrapleural lining, periosteum, and intercostal bundles. It is sutured to the mediastinum at the level of the hilus.

This type of modified thoracoplasty conversion has certain advantages over the usual staged procedure. It is planned as a two-stage procedure; paradoxical movement of the chest wall is avoided. The second and more extensive stage is performed on a patient whose sputum has been "converted" and may be delayed if there are complications. Finally, preservation of the first rib and transverse processes produces a better cosmetic result (figures 4, 6, and 7).

The collapse is not so complete, however, and lacks the permanence of the standard staged thoracoplasty because the apex of the lung tends to creep up in spite of the sutured periosteal flap. Since extrapleural pneumonolysis constitutes the first stage, the operation carries with it all of the difficulties of management and all of the complications of extrapleural pneumothorax. The writers have used this procedure for unilateral, moderately advanced disease with small or thin-walled, non-peripheral cavities in patients for whom a good cosmetic result was particularly important, especially if the operation was performed during the growing years.

The operation, although it produced good results, was abandoned when it was found that subcostal-extraperiosteal Lucite sphere plombage achieved the same ends with fewer complications and less exacting postoperative care. Lobectomy is now used in some patients who previously would have been subjected to this type of thoracoplasty modification.

Complications

The complications of extrapleural pneumonolysis were of two types, which have been designated *minor* and *serious*.

Minor complications: The minor complications were annoying and required a great deal of time and care for their treatment and correction, but they did not interfere with the eventual management of the space and successful outcome of the operation. The various complications are summarized in table 2. Of 47 pneumonolyses, 14 per cent were followed by such minor complications.

Three patients developed extrapleural hematomas which were successfully treated with streptokinase-streptodornase (20).

One patient manifested the syndrome of superior vena caval obstruction immediately after each refill. The headache, swelling of the face, and the venous distention always disappeared within two to three hours.

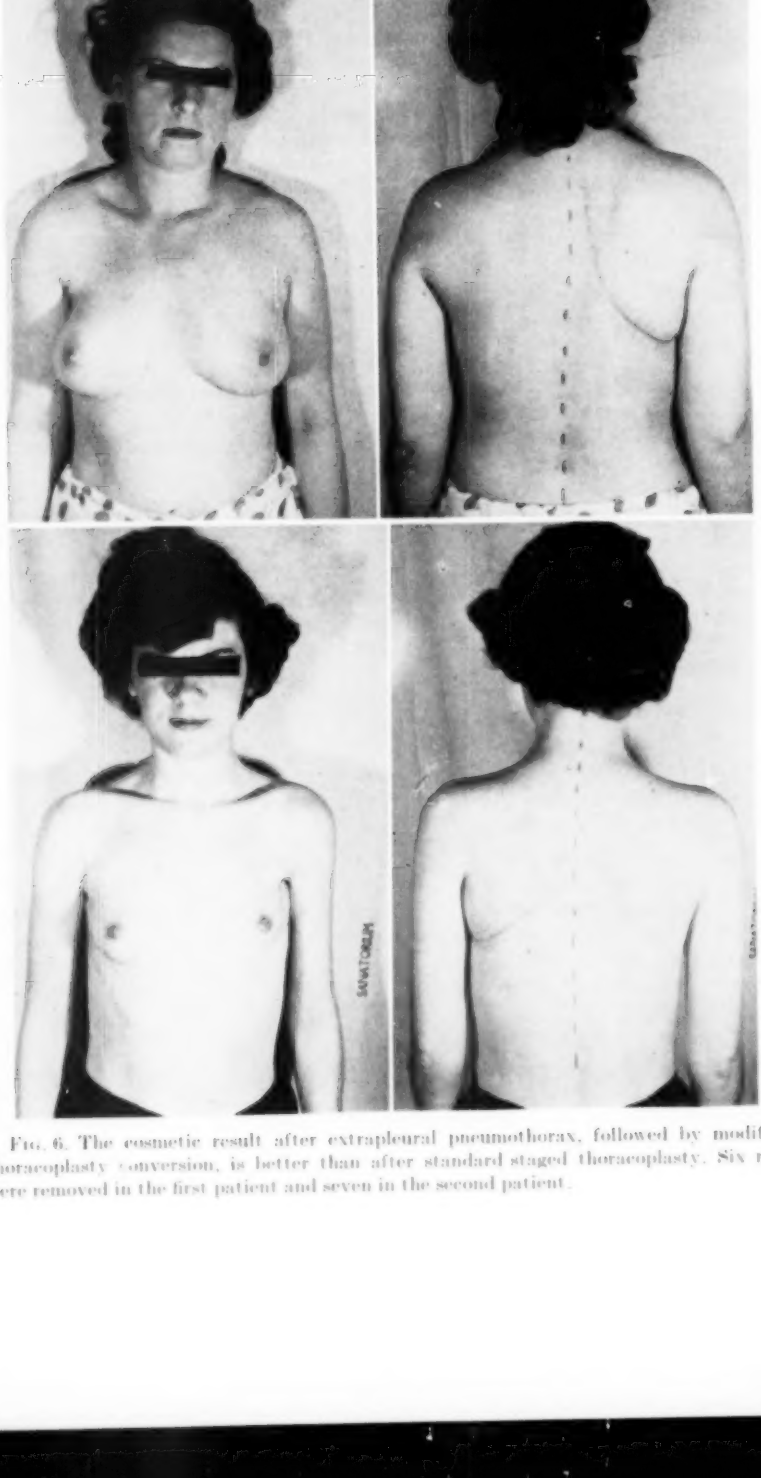

FIG. 6. The cosmetic result after extrapleural pneumothorax, followed by modified thoracoplasty conversion, is better than after standard staged thoracoplasty. Six ribs were removed in the first patient and seven in the second patient.

One patient had a persistent communication between the extrapleural and subcutaneous spaces directly under the incision. An annoying bulge persisted

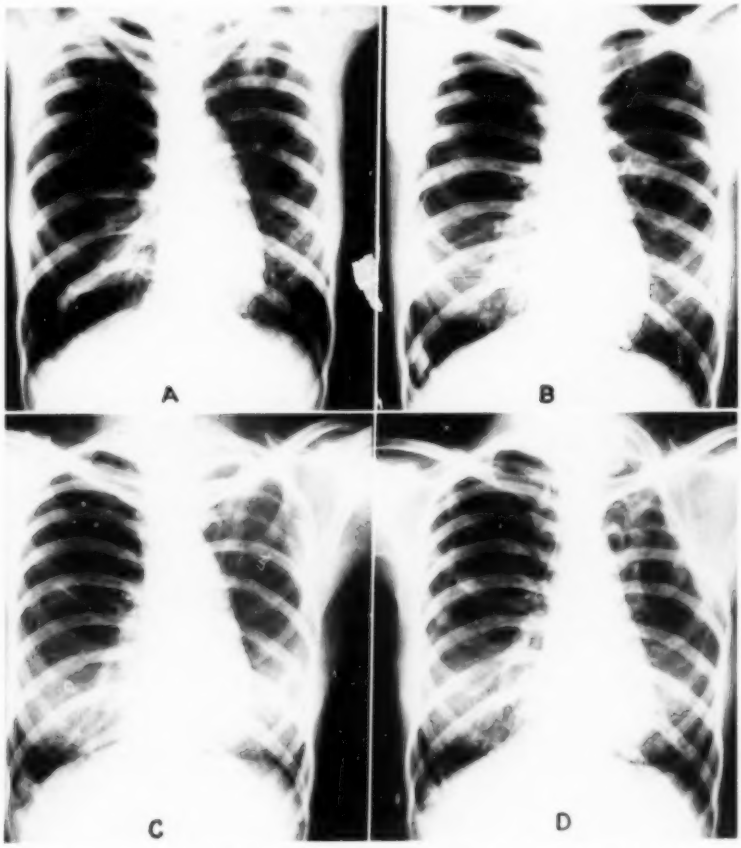

FIG. 7. Roentgenograms of the chest of a 26-year-old woman. Intrapleural pneumothorax was induced on the right because of a small apical cavity. Pneumothorax was attempted on the left for a similar cavity but no space could be found (*A*). Extrapleural pneumothorax failed for the commonest reason: the cavity dropped from the apex into the wider mid portion of the hemithorax (*B*). The posterior apical segment of the left lung was removed and the space was abandoned (*C*). The last roentgenogram was obtained after a small, space-reducing thoracoplasty (*D*).

after every refill for many weeks. The defect was easily identified at reoperation and was closed with a small muscle flap.

One minor air embolism occurred after a refill but had no permanent sequelae.

Serious complications: Serious complications occurred in 16 per cent of the patients (table 2) and eventually compelled the abandonment of the space.

Accidental opening of the pleural space was not usually followed by other complications. It did make the management somewhat more difficult during the first few postoperative days and, to some extent, nullified the function-sparing characteristics of the operation (18). In 2 patients this accident led to a permanent intra-extrapleural communication. Pulmonary function in both patients was such that the intrapleural pneumothorax, which recurred with every refill, was not well tolerated and the spaces had to be abandoned.

TABLE 2

COMPLICATIONS OF EXTRAPLEURAL PNEUMOTHORAX

COMPLICATION	NUMBER	PER CENT
A. *Complications which did not interfere with successful outcome of the operation*		
1. Extrapleural hematoma successfully treated with streptokinase-streptodornase	3	6
2. Operative spread of disease	1	2
3. Superior vena cava syndrome after refills	1	2
4. Extrapleural subcutaneous air fistula requiring secondary closure	1	2
5. Minor air embolism	1	2
Total, minor complications	7	14
B. Complications which led to abandonment of space		
I. *Early*		
1. Pleura opened during operation*, permanent intra-extrapleural communication	2	4
2. Loss of space due to difficulties of maintenance	1	2
3. Excessive subcutaneous emphysema (poor closure)	1	2
4. Extrapleural hematoma before streptokinase-streptodornase became available	3	6
II. *Late*		
1. Extrapleural tuberculous empyema	1	2
Total, major complications	8	16
TOTAL, all complications	15	30

* Inadvertent opening of the pleura at operation without further complications was not included. This accident nullifies to some extent the function-sparing characteristics of the operation (18). It always makes the postoperative management more difficult.

One patient with severe pulmonary emphysema and a contralateral ten-rib thoracoplasty required hourly refills during the immediate postoperative period. In spite of this, the lung became adherent at the apex. The space was maintained for a while by air injections posteriorly through the second interspace but finally it had to be abandoned.

Poor wound closure in one patient resulted in severe subcutaneous emphysema, and refills were discontinued for one week. Attempts to re-establish the space failed because the lung had become adherent.

Three patients developed an extrapleural hematoma before streptokinase-streptodornase became available. Unsuccessful attempts were made to liquefy the clot with saline, azochloramide, and hydrogen peroxide. Collapse by standard staged thoracoplasty was necessary in all 3 patients (20).

Extrapleural tuberculous empyema, the only serious late complication (table 2), occurred in one patient. The space was closed by a standard thoracoplasty and recovery was uneventful.

Therapeutic Results

Analysis of the early results, summarized in table 3, showed that 32 patients were discharged six months to one year after operation without supplementary

TABLE 3

EARLY RESULTS OF EXTRAPLEURAL PNEUMOTHORAX AND SUPPLEMENTARY PROCEDURES

	NUMBER OF FAILURES	NUMBER WELL
Primary operation	15	32
Technical failures (7)		
1. Converted to standard thoracoplasty		3
2. Converted to subcostal plombage		3
3. Abandoned	1	
Extrapleural empyema (1)		
1. Converted to standard thoracoplasty		1
Failure of cavity closure (5)		
1. Lower lobectomy, extrapleural space maintained		1
2. Upper lobe segmental resection, extrapleural space abandoned	1	
3. Upper lobectomy, space abandoned		1
4. Abandoned (one bilateral expl.)	2	
Patients eloped, space abandoned	2	
Total number of group, discharged well with extrapleural pneumothorax and supplementary operations in some		41
Percentage of group, discharged well		84 per cent

procedures. Extrapleural pneumothorax alone was thus responsible for reversal of infectiousness in 66 per cent of the group.

Of the 7 patients in whom the space could not be maintained, 3 were treated by standard thoracoplasty, 3 by subcostal-extraperiosteal plombage, and the lung was allowed to re-expand in one patient because pulmonary insufficiency did not permit modification of the collapse by thoracoplasty.

In 5 cases, cavities persisted. This was always due to dropping of the cavity from the narrow apex of the thorax into its wider midportion (figures 7 *A* and *B*). In view of this, the advisability of mediastinal dissection to the hilum has been questioned recently. In one of the 5 patients, no further attempt at surgical therapy was made because of progressive bilateral excavation. A second patient with

lower lobe cavitation had a right lower lobectomy one year after pneumonolysis when laminagraphy showed a persistent cavity (figure 5 *C*). The extrapleural space was maintained (figure 5 *D*). A small apical cavity dropped with the apex in another patient but failed to close (figure 7 *B*). A resection of the left posterior apical segment was performed and the space was abandoned (figures 7 *C* and *D*). Finally, one patient of *Group II*, who had extrapleural pneumothorax as a first stage to modified thoracoplasty, had gastric washings intermittently positive

TABLE 4

LATE FOLLOW-UP AFTER EXTRAPLEURAL PNEUMONOLYSIS WITH AND WITHOUT SECONDARY OPERATIONS

44 Patients (47 Operations), One to Three and One-half Years

	NUMBER	PER CENT
Lesions arrested, patient at home	37	84
Employed full time or full time housework	(30)	
Resting or part time work	(7)	
Unimproved, at home	1	2
Unimproved, hospitalized	2	5
Dead	4	9
Eloped, space abandoned, died of pulmonary tuberculosis, malnutrition, delirium tremens, and portal cirrhosis	(2)	
Technical failure, disease arrested by thoracoplasty; discharged well with some dyspnea. Died of cor pulmonale and pulmonary edema one year after discharge. Post-mortem examination revealed no active tuberculosis	(2)	

TABLE 5

EVENTUAL MANAGEMENT OF 32 ESTABLISHED EXTRAPLEURAL SPACES

	NUMBER	PER CENT
Converted by modified thoracoplasty	16	53
Converted by standard thoracoplasty	3	9
Initial plastic sphere plombage	1	3
Extrapleural space maintained	11	35
Because of insufficient pulmonary reserve for thoracoplasty	(8)	
Patient refused thoracoplasty	(3)	

for tubercle bacilli after the second stage. Residual cavities were treated by upper lobectomy.

Two patients, both alcoholics, eloped from the hospital. Neither returned for refills, and both were admitted to the Boston City Hospital four to six months afterwards. At that time both patients had far advanced bilateral tuberculosis complicated by delirium tremens and malnutrition. Both died shortly after readmission.

Of the 47 operations, 66 per cent were successful. The percentage of well patients was raised to 87 by various supplementary surgical measures.

One to three and one-half years after operation, 37 of the 44 patients (84 per

cent) were at home and well (table 4). Three patients were hospitalized and had sputum positive for tubercle bacilli. Four patients were dead. Two of these died of cor pulmonale and pulmonary edema one year after bacteriologic "conversion" by extraperiosteal-subcostal plombage.

It is believed that the maintenance of an extrapleural air space presents potential hazards of infection and loss of the space, and every effort has been made to avoid continued refills. The eventual management of the space of 31 patients who were successfully operated on are shown in table 5. The space was converted by modified thoracoplasty in patients in whom this was planned originally and in patients who had contralateral disease which healed during the postoperative convalescence. In 11 patients the space was maintained because pulmonary function was so poor that thoracoplasty was contraindicated or because they refused further surgery. In one patient, in whom the operation was performed because of repeated massive hemorrhage and bilateral disease, the space was filled with Lucite spheres following pneumonolysis. This 64-year-old man has been well at home for three years. Conversion to oleothorax has not been used in this series.

DISCUSSION

Previous reports of extrapleural pneumonolyses have stressed the occurrence of extrapleural empyema, which complicated 13 to 45 per cent of the cases, and various fistulous formations in relation to the contiguous structures which occurred in 5 to 14 per cent (3–13, 21, 22). The incidence of these accidents was expected to diminish with use of antimicrobial therapy and, indeed, some early results have confirmed this expectation. Le Foyer and associates reported empyema in 45 per cent of 33 patients operated upon without streptomycin and in 3 per cent of 32 patients who received the drug (21). Cutler similarly divided his series and has reported no empyema or bronchopleural fistula in a few patients operated upon since the advent of streptomycin (22). In the present series, nontuberculous infections, bronchopleural and broncho-esophageal fistulas were not encountered; and extrapleural tuberculous empyema, seen on a single occasion, was readily controlled by chemotherapy and thoracoplasty conversion. It was thought that antimicrobial therapy was the single most important factor in reducing the hazards of the operation.

The problem of extrapleural hemorrhage has been given a great deal of attention in the literature (1, 2, 5, 6, 8, 20, 22). The sudden, often unexpected loss of blood which may occur many hours after operation has been responsible for a number of operative fatalities, particularly if anticoagulants were placed in the space (4, 6, 8). Readily available bank blood has relegated these accidents to the group of minor complications.

The formation of extrapleural hematoma has been cited as a common complication in most large series and was by far the most frequent complication among the writers' patients (table 2). In the past this has frequently led to abandonment of the space, as it did in 3 patients of the present series, before fibrinolytic enzymes could be obtained. Anticoagulant therapy and reoperation have not been

satisfactory remedies. The availability of pure and nontoxic substrates for enzymatic fibrinolysis has eliminated extrapleural clot formation as a cause of operative failure. The writers' experiences in this regard (20) have coincided with those of Cutler (22). With streptokinase-streptodornase, a satisfactory extrapleural space was established in every case in spite of massive clot formation (table 2).

The initial enthusiasm for extrapleural pneumonolysis was based, to a large extent, on the clinical observation that the operation is more "selective" than thoracoplasty. The function-sparing characteristics of pneumonolysis have been confirmed (24) and amplified by bronchospirometric studies (18, 25). It was found that the operation could be used in patients with severe ventilatory insufficiency (figure 2). Routine preoperative evaluation by means of pulmonary function tests and differential bronchospirometry has permitted operation in a number of patients who heretofore had been refused surgery because of clinical dyspnea. Pulmonary "crippling" and operative fatalities due to respiratory insufficiency have been entirely avoided by this type of preoperative evaluation (table 2).

At first, pneumonolysis was performed under local anesthesia (1, 2) and many surgeons have continued its use (4, 5, 12). Formerly, this type of anesthesia had the considerable advantage that patients were able to raise secretions during and immediately after the operation, and the clinical course could be more closely observed. Today, endotracheal tubes permit removal of secretions during general anesthesia and intermittent positive pressure breathing permits control of ventilation and depth of anesthesia. The better exposure, the shorter operative time, unhindered by uncontrolled pulmonary movement due to cough, and the lessened psychic trauma of general anesthesia need no longer be sacrificed. Complications which occur during the operation, such as injury to intercostal vessels and accidental tearing of the pleura, are handled with greater facility under general anesthesia with endotracheal intubation.

The present writers have learned much from the unfortunate previous experiences of others with regard to the use of the operation in subpleural cavitation and the use of plastic substances in the extrapleural space. The absence of major complications in the present series was attributed, to a great extent, to the exclusion of patients with peripheral cavities. This point, repeatedly mentioned by others, cannot be overemphasized (4, 8, 10, 12, 13). Extrapleural pneumothorax has been avoided whenever there were large, thin-walled cavities in relation to the parietal pleura, and in the present series the development of the extrapleural space was possible without force or extensive sharp dissection.

As a result of these considerations, it has been concluded that extrapleural pneumothorax has a definite place in the treatment of pulmonary tuberculosis. In the writers' experience, the operation is the procedure of choice for patients with pulmonary insufficiency due to previous collapse or resection on the opposite side and for patients for whom surgical treatment of the other lung is anticipated in the near future. As a result, certain desperately ill patients, for whom no other procedure is suitable, are returned to useful activity by extrapleural pneumotho-

rax. The operation can be performed in selected cases with a very low mortality and with few serious complications.

In "good-risk" patients, with adequate pulmonary function and unilateral disease, the operation is not indicated because other types of collapse or resection offer as good or better therapeutic and cosmetic results with fewer minor complications and less time-consuming and exacting postoperative care.

SUMMARY

In the light of recent medical and surgical advances, a renewed appraisal of extrapleural pneumonolysis and a clarification of its current place in the therapeutic armamentarium appeared indicated.

The operation was used in two groups of patients: first, those who had pulmonary insufficiency due to previous contralateral collapse or resection or to bilateral cavernous disease; second, a smaller group of "good-risk" patients for whom a good cosmetic result was sought. In this latter group, the operation was used as a first stage of a modified thoracoplasty. Because of the narrow indications, only forty-seven operations, constituting 14 per cent of the entire operative experience, were performed over a period of four years.

There was no operative mortality and only 16 per cent of the operations were followed by major complications. No fistulas were encountered, and extrapleural empyema occurred in one case.

Sixty-six per cent of the patients were clinically well and abacillary without other surgical procedures. A one-year follow-up showed that 84 per cent of all patients were well after extrapleural pneumothorax alone or after secondary thoracoplasty or resection.

Extrapleural pneumothorax is the procedure of choice in "poor-risk" patients with pulmonary insufficiency. In "good-risk" patients with unilateral disease, the operation is not indicated because subcostal-extraperiosteal plombage or resection offer as good or better results with fewer complications.

SUMARIO

Neumotórax Extrapleural

A la luz de los recientes adelantos médicos y quirúgicos, parecian indicados una nueva justipreciación de la neumonolisis extrapleural y el esclarecimiento del papel que le corresponde actualmente en el arsenal terapéutico.

La operación fué usada en dos grupos de enfermos: primero, en los que tenian insuficiencia pulmonar debida a previo colapso contralateral o a resección o a cavernas tuberculosas bilaterales; segundo, en un número más pequeño de sujetos que constituían "buenos riesgos" y en los que se busca buen efecto estético. En este último grupo, se empleó la intervención como primer tiempo de una toracoplastia modificada. Debido a las limitadas indicaciones, no se ejecutaron más que cuarenta y siete operaciones, que representaron 14 por ciento del total de cirugía, en un periodo de cuatro años.

No hubo mortalidad operatoria y sólo 16 por ciento de las intervenciones fueron seguidas de complicaciones de mayor cuantía. No se observaron fistulas y ocurrió empiema extrapleural en un caso.

Sesenta y seis por ciento de los pacientes fueron dados de alta clínicamente bien sin más procedimientos quirúrgicos. Una observación subsecuente de un año reveló que 84 por

ciento de todos los enfermos se encontraban bien, ya después del neumotórax extrapleural solo o de la toracoplastia o resección secundaria.

El neumotórax extrapleural es el procedimiento de elección en los enfermos con insuficiencia pulmonar que constituyen "malos riesgos." En los sujetos con enfermedad unilateral, que son buenos riesgos, no está indicada dicha operación, porque el plombaje subcostal extraperióstico o la resección dan resultados tan buenos o mejores con menos complicaciones.

RESUME

Pneumothorax extra-pleural

A la lumière des récents progrès médicaux et chirurgicaux, il a paru indiqué de procéder à la ré-évaluation de la pneumolyse extra-pleurale et à la clarification de sa position actuelle dans l'arsenal thérapeutique.

Deux groupes de malades ont été soumis à l'intervention: primo, ceux qui présentaient une insuffisance de la fonction pulmonaire due à un collapsus antérieur ou à une résection du côté opposé ou à des spélonques bilatérales; secundo, un groupe plus réduit, composé de malades représentant "un bon risque opératoire" pour lesquels on désirait obtenir un résultat esthétique satisfaisant. Dans ce dernier groupe, l'opération représentait le premier stade d'une thoracoplastie modifiée. En raison d'indications limitées, il n'a été pratiqué que quarante-sept interventions en quatre ans, soit 14 pour cent de l'expérimentation chirurgicale totale.

La mortalité opératoire a été nulle et seulement 16 pour cent des opérations ont présenté des complications importantes. Aucune fistulisation ne s'est produite et l'empyème extra-pleural a été observé dans un seul cas.

A la sortie de l'hôpital, la guérison clinique sans autre procédé chirurgical était obtenue chez 66 pour cent des malades. L'observation de ces malades, pendant un an, a permis de constater que 84 pour cent d'entre eux demeuraient en rémission après le pneumothorax extra-pleural seul, ou après la thoracoplastie secondaire ou la résection.

Le pneumothorax extra-pleural est la méthode de choix à utiliser dans les mauvais cas avec insuffisance de la fonction pulmonaire. Dans les "bons risques" avec atteinte unilatérale, cette intervention n'est pas indiquée, car le plombage extra-périosté subcostal ou la résection donnent des résultats au moins aussi bons, ou meilleurs, avec moins de complications.

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INTERMEDIARY REPORT OF 102 STREPTOMYCIN-PROTECTED PULMONARY RESECTIONS[1, 2, 3]

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(Received for publication May 28, 1952)

INTRODUCTION

After the introduction of streptomycin in 1945, there was a resurgence of pulmonary resection as a definitive therapeutic procedure for tuberculosis. The high incidence of postoperative complications such as spread of disease, empyema, and bronchopleural fistula prior to that date had caused many surgeons to abandon the procedure. Numerous early reports dealing with the use of streptomycin as an adjunct to surgery have been made. All agree that both morbidity and mortality rates have been favorably influenced. Final judgment of the place of streptomycin in a surgical program will depend upon the results after a lapse of five or ten years. An intermediary report dealing with a rather large group of patients who have been followed from three to six years after resection may be of value at this time.

OBSERVATIONS

The present report consists of follow-up observations on 102 resections in 100 patients operated on during the period from October 2, 1945, to December 8, 1948. None of the patients had been given streptomycin prior to resection. All were given the drug for one week preoperatively and two weeks postoperatively. Resections were limited almost entirely to pneumonectomies and lobectomies. In an occasional case, a diseased segment was also removed at the time of lobectomy.

Forty-nine patients had lobectomies and 51 had pneumonectomies. A secondary resection was done on 2 lobectomy patients. The average age for the entire group was 30.2 years. Only 2 patients were females. Twenty-nine were Negroes. Indications for resection (table 1) were those in common use. Forty-one of the operations were performed because of a thoracoplasty failure.

Follow-up study of these patients was done at the Oteen or at other Veterans Administration clinics.

Forty-one of the pneumonectomy patients (80.4 per cent) have had complete follow-up observations from operation to date. The shortest period of observation in living patients was 36 months; the longest, 59 months. Ten patients had in-

[1] From the Veterans Administration Hospital, Oteen, North Carolina.

[2] Presented before the Medical Session, as part of the *Surgical Session on Tuberculosis*, at the 48th annual meeting of the National Tuberculosis Association, Boston, Massachusetts, on May 28, 1952.

[3] Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

complete follow-up observations but were observed for an average period of 21.5 months after operation.

Forty-five of the lobectomy patients (91.9 per cent) had complete follow-up observations. The living patients were followed for 36 to 72 months. Four patients have incomplete follow-up studies, which averaged 24 months.

TABLE 1

INDICATION FOR RESECTION

Pneumonectomies:	
1. Thoracoplasty failure	21
2. Extensive unilateral disease	12
3. Destroyed lung	7
4. Tuberculous bronchiectasis	5
5. Failure of conservative collapse measures	5
6. Tuberculous empyema with nonexpansible lung	1
Lobectomies:	
1. Thoracoplasty failure	20
2. Elective procedure	9
3. Failure to respond to conservative measures	6
4. Tuberculous bronchiectasis	5
5. Hydropneumothorax with unexpanded lung	3
6. Undiagnosed lesion	3
7. Lower lobe cavity (nonresponsive to conservative therapy)	2
8. Recurrent cavity	2
9. Bronchostenosis	1

TABLE 2

CAUSES OF DEATH

Pneumonectomies:
- *Early:*
  1. Cerebral anoxia due to operative hemorrhage
  2. Operative—hemorrhage (uncontrollable)
  3. Tuberculous pericarditis with tamponade
- *Late:*
  1. Tuberculous meningitis
  2. Diabetic coma

Lobectomies:
- *Early:*
  1. Postoperative pulmonary edema (13 days)
  2. Postoperative pulmonary embolism (3 days)
  3. Cardiac arrest in operating room
  4. Postoperative hemorrhage (1 hour)

Deaths: There have been 9 deaths (8.8 per cent of the series) up to the present time (table 2). Seven of the deaths occurred early and 2, late. In the 51 pneumonectomy patients there were 5 deaths (9.7 per cent). In 3 instances, or 5.8 per cent of the series, the deaths were operative. One patient died from operative hemorrhage, one from cerebral anoxia due to hemorrhage, and one from

tuberculous pericarditis and tamponade sixteen days postoperatively. Death occurred late after the operation in 2 patients, or 3.9 per cent of the group. One of these deaths resulted from tuberculous meningitis five months postoperatively; the other occurred at home from diabetic coma in a patient whose tuberculosis was apparently arrested.

The 4 lobectomy deaths (7.8 per cent) were all operative. There have been no late deaths in this group of patients. One died of pulmonary embolism, another of cardiac arrest, the third of pulmonary edema, the fourth of postoperative hemorrhage.

Complications: The important early complications in this series have been related to the problem of tuberculosis (table 3). Bronchopleural fistula occurred following 9 (17.6 per cent) operations in the pneumonectomy series. The 2 late

TABLE 3

COMPLICATIONS (PNEUMONECTOMIES)

	NUMBER	PER CENT
Early:		
1. Bronchopleural fistula	9	17.6
2. Empyema	2	3.9
3. Tuberculous pericarditis	2	3.9
4. Pneumonitis (nonspecific)	1	1.9
7. Spread of disease	1	1.9
Total	15	29.2
Late:		
1. Reactivation	3	5.8
2. Extrapulmonary tuberculosis	2	3.9
3. Tuberculous endobronchial disease (stump)	1	1.9
4. Tuberculous wound abscess	3	5.8
Total	9	17.4

deaths occurred in this group. In 6 of the other 7 patients, the fistula was closed after numerous surgical procedures. In the seventh the fistula closed but subsequently reopened, with a resultant spread of disease to the opposite lung. The development of a fistula is usually associated with an increase in morbidity and mortality, usually from pulmonary or extrapulmonary spread of the tuberculosis.

Two of the pneumonectomy patients (3.9 per cent) developed tuberculous empyemas unrelated to a bronchopleural fistula. In both, the pleural infection has subsided. Two patients (3.9 per cent) developed tuberculous pericarditis, one with tamponade. The latter died sixteen days postoperatively; the other made an uneventful recovery. One spread of tuberculosis occurred in a patient who had developed a bronchopleural fistula. The fistula closed and his pulmonary lesion is now stable. One patient developed a nonspecific pneumonitis which rapidly cleared.

Late complications in the pneumonectomy cases were: reactivation, extrapulmonary tuberculosis, tuberculosis of bronchial stump, and tuberculous wound abscess.

Reactivation occurred at 2, 5, and 16 months, respectively, in 3 (5.8 per cent) of the patients. One is hospitalized because of a bronchopleural fistula. In the other 2, the disease has been controlled. Two (3.9 per cent) developed extrapulmonary tuberculosis. One died of meningitis at 5 months following a bronchopleural fistula and spread of disease. The other developed tuberculosis of the spine 43 months following his resection and is now hospitalized. One patient was found to have endobronchial disease of the stump at 8 months. The lesions healed

TABLE 4

COMPLICATIONS (LOBECTOMIES)

		NUMBER	PER CENT
Early:			
1. Bronchopleural fistula		1	1.9
2. Empyema		1	1.9
3. Postoperative psychoses		1	1.9
4. Spread of disease		2	3.8
5. Pneumonitis (nonspecific)		1	1.9
Total		6	11.4
Late:			
1. Reactivation		12	23.5
ipsilateral	4		
contralateral	7		
bilateral	1		
2. Endobronchial disease		1	1.9
3. Extrapulmonary tuberculosis		2	3.9
4. Tuberculous wound abscess		2	3.9
5. Hemoptysis		2	3.9
Total		19	37.2

with streptomycin therapy. Three tuberculous abscesses of the wound developed at 7, 23, and 24 months. All 3 have healed wounds at present.

Early complications (table 4) were fewer in the lobectomy series. Bronchopleural fistula occurred in only one patient. This man also developed a contralateral spread of disease which stabilized after closure of the fistula. One other patient developed a contralateral postoperative spread of disease. The lesion regressed but a cavity developed on the ipsilateral side 17 weeks postoperatively. The patient died of cardiac arrest during a secondary operation. One patient developed an empyema which responded to open thoracotomy and thoracoplasty. Contralateral nonspecific pneumonitis, which cleared rapidly in a few days, occurred in one patient. One patient developed a postoperative psychosis, which responded to psychotherapy.

The serious late complication in the lobectomy cases was reactivation or spread of disease. This occurred in 12 patients 4 to 43 months after operation. Two of these patients died following secondary operation. One recently had a pneumonectomy with removal of the remaining lobes of the previously operated upon lung; one is being rehabilitated at present; and 5 are hospitalized with active disease. Endobronchial disease, which responded to treatment, occurred in one patient. Extrapulmonary tuberculosis developed in 2 patients, or 3.9 per cent of the group. Tuberculous meningitis which developed two months postoperatively in one patient was apparently cured by chemotherapy. In another instance,

TABLE 5

RESULTS OF SPUTUM EXAMINATIONS FOR TUBERCLE BACILLI

	COMPLETELY NEGATIVE		INFREQUENTLY POSITIVE		CURRENTLY NEGATIVE	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Pneumonectomy	35	68.6	10*	19.6	45	88.2
Lobectomy	27	55.1	13†	26.5	40	81.6
Total	62	62	23	23	85	85

* 3 patients had only one positive examination.
† 4 patients had only one positive examination.

TABLE 6

PRESENT STATUS OF PATIENTS

	NUMBER	PER CENT
Pneumonectomies:		
Discharged	42	82.3
Hospitalized	4	7.9
Dead	5	9.8
Lobectomies:		
Discharged	38	77.5
Hospitalized	7	14.3
Dead	4	8.2

a tuberculous anal fistula closed. Late tuberculous wound abscesses developed in 2 patients. These wounds healed after excision with streptomycin protection. Two patients with an associated bronchiectasis had hemoptysis at 5 and 7 months; no further treatment was required.

Bacteriologic findings: Review of this group of patients (table 5) shows that, following 35 pneumonectomies, or in 68.6 per cent of the operations, the sputum has been negative for tubercle bacilli from the date of operation. Ten patients discharged tubercle bacilli intermittently during the period of follow-up observation. At present, 45 patients (88.2 per cent of the pneumonectomy cases) have sputum which is negative for *M. tuberculosis*. The one patient whose sputum

remains positive for tubercle bacilli has a fistula which reopened and was followed by spread of disease to the opposite side.

Twenty-seven of the lobectomy patients (55.1 per cent) have had sputum negative for tubercle bacilli from the date of their operation. Thirteen (26.5 per cent) have discharged bacilli intermittently. At present, 40 patients (81.6 per cent) have sputum negative for *M. tuberculosis*. The 5 patients with a "positive sputum" are those in whom late reactivation of the tuberculosis occurred and they are hospitalized at present.

At the present time (table 6) 43 (84.3 per cent) of the pneumonectomy patients have been discharged. Three (5.8 per cent) are still hospitalized. One patient is being treated for tuberculosis of the spine; one is at the rehabilitation center and will soon be discharged; the last is hospitalized elsewhere, under treatment for a bronchopleural fistula with spread of disease.

Thirty-eight of the lobectomy patients (77.5 per cent) have been discharged. Five are hospitalized, receiving active treatment for late spreads of their tuberculosis. One is at the rehabilitation center following clearing of a late "spread," and one is convalescing from a secondary resection of the remaining lobes of his right lung for a late progression with cavitation which was resistant to other measures.

DISCUSSION

Analysis of the data obtained in this study substantiates the early impressions that pulmonary resection can be done with a reasonable morbidity and mortality. These patients were operated upon during the pioneer days of resection. Four deaths were due to catastrophes in the operating room. It would seem reasonable to believe that improvements in surgical technique and methods of anesthesia should result in a lower mortality rate. This has been true in regard to operative mortality. The decrease in the total mortality rate, however, has not been as definite. There were at least two reasons for this: first, enthusiasm engendered by the early successes resulted in too wide an extension of the indications for resection; second, the patients under consideration represented a rather unique group. Forty-one per cent had successfully undergone thoracoplasties. None of them had received chemotherapy prior to their resection course of three weeks. In view of the present concepts of the necessity for long-term chemotherapy, it seems likely that these patients must have had a definite inherent native resistance which permitted them to survive until resection and streptomycin were available.

Postoperative bronchopleural fistula and late reactivation of disease are the major problems which remain to be solved. Careful case selection and long-term chemotherapy before and after surgery seem to offer the best hope for solution of these problems. It is the present practice to give one of the many agents now available for a long enough period before operation to result in a stabilization of the lesion. Impressions as to the stability of the lesion in the roentgenographic series are coordinated with the histologic report. It is hoped there will be seen in the microscopic section broad zones of fibrosis with minimal specific granulation

tissue and an absence of areas of tuberculous pneumonia in the surrounding pulmonary parenchyma. Many of the present patients have been under treatment with streptomycin or other drugs for several months on the medical wards before being referred for surgery. Others not under treatment are given chemotherapy for at least two months prior to therapy. The treatment is continued for at least sixty days after operation, and a determination is then made of the needs for further treatment.

SUMMARY

The immediate results following pulmonary resection for tuberculosis were proved to be satisfactory in many reported series. The present study offers some evidence that the intermediate results are also satisfactory. A total case mortality rate of 9.0 per cent was observed. When balanced against the fact that 85 per cent of this group have a sputum negative for *M. tuberculosis* at the end of three years, it can be seen that the procedure has a great deal of merit.

SUMARIO

Comunicación Intermedia sobre 102 Resecciones de Pulmones Protegidos con Estreptomicina

Los resultados inmediatos consecutivos a la resección pulmonar por tuberculosis se han mostrado satisfactorios en muchas series descritas. El estudio actual ofrece algunas pruebas de que los resultados intermedios son también satisfactorios. La mortalidad total observada fué de 9.0 por ciento. Contrapesada con el hecho de que 85 por ciento de ese grupo tiene esputo negativo para el *M. tuberculosis* al cabo de tres años, puede verse que el procedimiento posee mucho mérito.

RESUME

Rapport intermédiaire sur 102 résections pulmonaires effectuées sous la protection de la streptomycine

Selon le rapport publié, les résultats immédiats de résections pulmonaires pour tuberculose se sont montrés satisfaisants dans un grand nombre des séries. Cette étude présente certaines données montrant que les résultats de la période intermédiaire sont également satisfaisants. Le taux de mortalité totale observé a été de 9%. Si on considère le fait qu'au bout de trois années on a trouvé chez 85% des sujets de ce groupe des crachats négatifs pour *M. tuberculosis*, la valeur de ce procédé paraît importante.

BRONCHIECTASIS: A COMPARATIVE STUDY[1]

JOSEPH GORDON AND PHILIP C. PRATT

(Received for publication February 4, 1952)

INTRODUCTION

In a previous publication (1) it was pointed out that certain differences could be recognized when comparing tuberculous and nontuberculous bronchiectasis. Four points of comparison were made: (*1*) segmental lobar location, (*2*) bronchographic pattern difference, (*3*) difference in inspiration-expiration bronchogram films, and (*4*) pattern difference in both bronchi and pulmonary arteries of injected lung specimens. In addition, the histopathologic variations were also pointed out. However, the study was not illustrated. For purposes of clarification and to re-emphasize the points previously made, it seems desirable to present this material in an expanded and illustrated form.

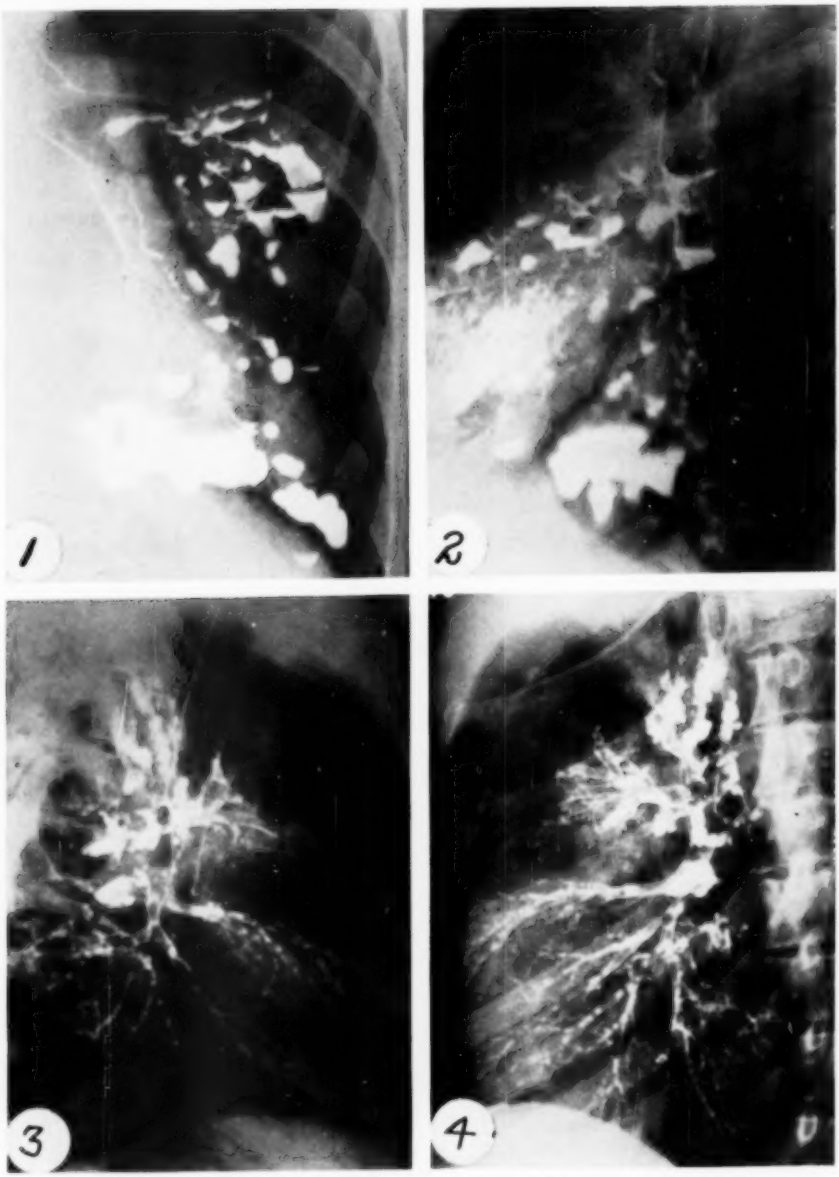
OBSERVATIONS

The more common localization of nontuberculous bronchiectasis in posterior and basal segments of the lung is noted by bronchography (figures 1 and 2). The contiguous lingular segment which is often involved on the left side, as the middle lobe may be on the other side, is also shown. In tuberculosis the bronchogram elicits the site of involvement as well, as was brought out in a publication elsewhere (2). The evidence of ectasia (figures 3 and 4) indicates the usual apical and posterior segmental localization. The not uncommon finding of disease in the contiguous superior segment of the lower lobe is noted as well.

A further study of these and other bronchograms (figures 5 and 6) reveals the fact that the dilated bronchi in nontuberculous disease extend to the margin of the shrunken lung. In tuberculosis the dilated bronchi distinctly do not extend to the periphery (figures 7 and 8) although the diseased portion of the lung is contracted. Moreover, a difference is also noted when bronchographic studies are made in both inspiration and expiration. In tuberculosis (figures 7 and 8), the bronchial lumen is seen to decrease in size in expiration, but little if any change is noted in nontuberculous disease (figures 5 and 6).

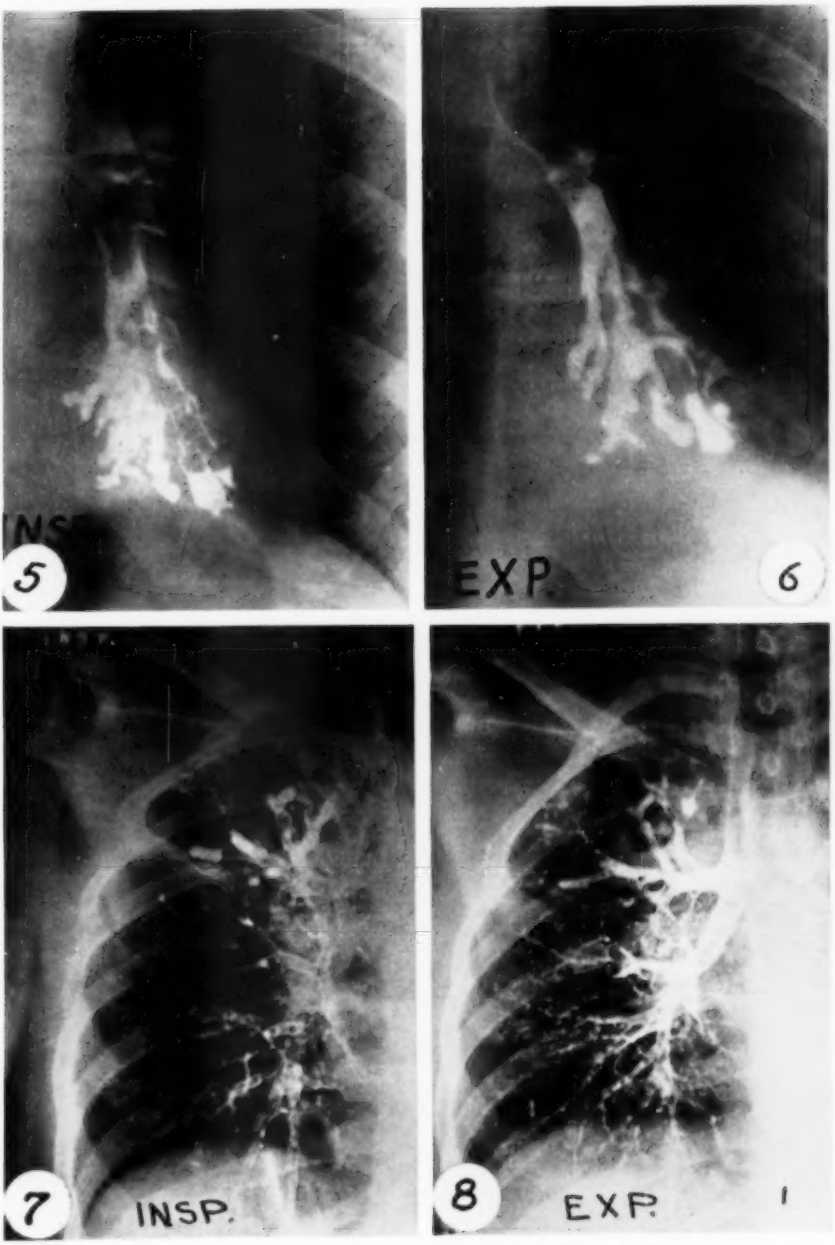
In a study of removed lung tissue in which bronchi and pulmonary arterial systems are injected with contrast media, other differences are revealed. In the normal lung one notes a delicate treelike arborization in the bronchogram (figure 9). A similar pattern is seen for the injected pulmonary artery (figure 10). In classical nontuberculous bronchiectasis, the injected bronchi show the same dilated appearance (figure 11) as is seen in the living and they extend to the margin of the lung. The injected pulmonary artery in the area of disease, however, has a normal appearance (figure 12). In tuberculosis the pulmonary arterial system shows marked obliteration and many fewer branches (figure 13). The bronchi (figure

[1] From the Ray Brook State Tuberculosis Hospital, Ray Brook, New York.



FIGS. 1 and 2. Case 1. Bronchograms in nontuberculous disease showing involvement in lower lobe and lingular segment of upper lobe.

FIGS. 3 and 4. Case 2. Bronchograms in pulmonary tuberculosis showing abnormalities in apical and posterior segments of upper lobe and superior segment of lower lobe.



Figs. 5 and 6. Case 3. Bronchograms in nontuberculous disease showing dilatations to periphery and little change in expiration.

Figs. 7 and 8. Case 4. Bronchograms in pulmonary tuberculosis showing (*1*) lack of filling in outer one third and (*2*) decrease in caliber of bronchial shadow in expiration.

14), on the other hand, are dilated; cavities fill easily; and, again, as in the living, the outer area of the diseased lung shows absence of filling.

A review of the histopathology of these two different chronic lung diseases, not only shows their specific difference, but clarifies the roentgenographic findings. In nontuberculous disease (figures 15 and 16) the tubular system is primarily involved. The dilated bronchi extend from the hilum to the periphery of the lung. The lymph nodes are regularly very much enlarged. There are varying degrees of alteration in the mucosa, muscularis, elastic membrane, and cartilage, with some evidence of inflammation. The altered epithelium is a prominent feature. Al-

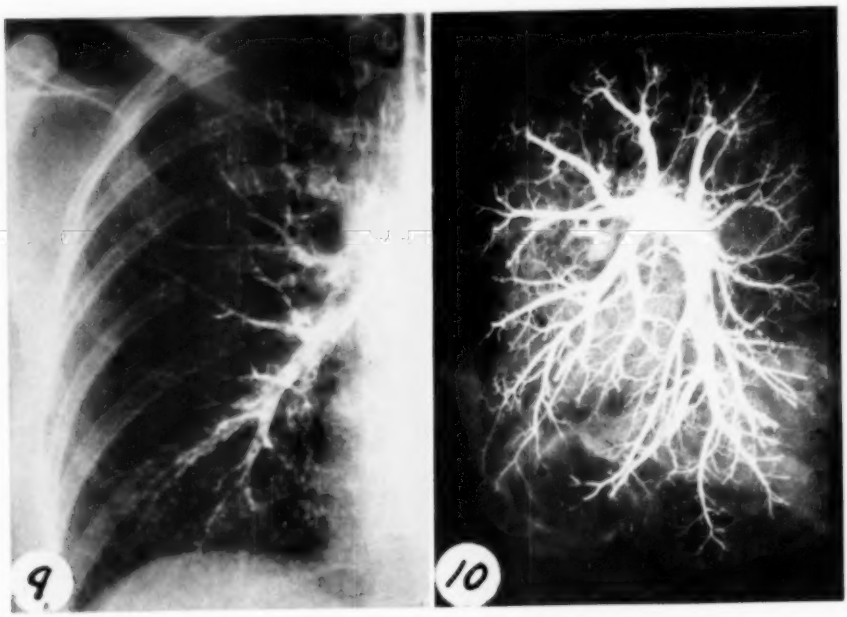


FIG. 9. Case 5. Normal bronchogram, living.
FIG. 10. Case 6. Normal pulmonary arteriogram, injected lung.

though pneumonia may be present at times, there is often little change in the lung parenchyma beyond collapse of alveoli in contiguous areas of the involved bronchi. The pulmonary arteries have a normal appearance, are thin-walled, and show no reaction despite extensive changes in the tubular system. From these findings, the bronchographic appearance becomes clear. The dilated involved tubular system in the bronchograms extends from the hilum to the distal portion of the lung and, being so damaged, cannot respond to respiratory movements.

In tuberculosis (figures 17 and 18) the involved areas of the lung show the characteristic pattern of necrotic lesions involving all parts of the parenchyma. In regions of dense scar tissue replacement, there is obliteration of the smaller

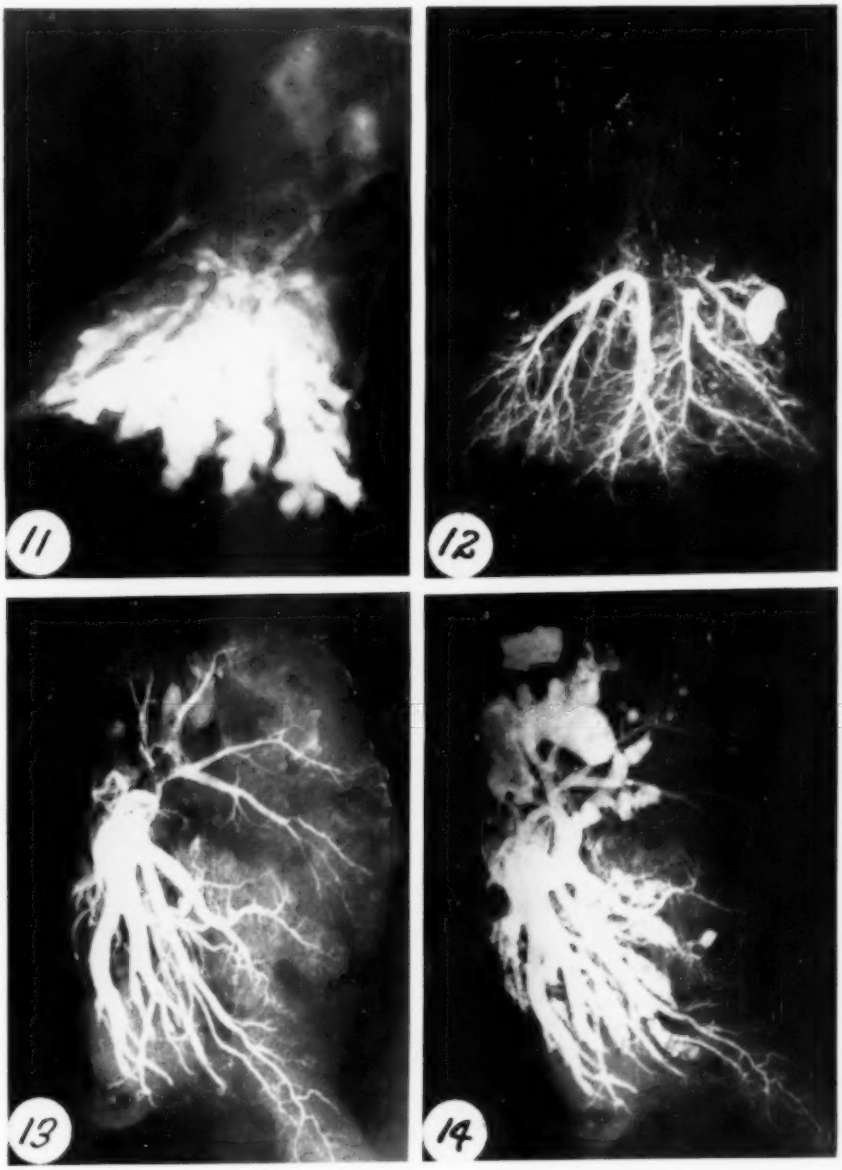


FIG. 11. Case 7. Bronchial tree injection in nontuberculous disease showing filling to periphery of lobe.

FIG. 12. Case 8. Pulmonary artery injection of similar specimen showing normal pattern in region of nontuberculous disease.

FIG. 13. Case 9. Pulmonary artery injection of surgically removed lung showing poor pattern in extensive tuberculosis.

FIG. 14. Case 9. Same lung with bronchi also injected showing limitation of bronchial filling similar to that seen in bronchogram during life.

arterial branches as well as of the bronchi and bronchioles. The bronchi toward the hilum are uninvolved, appear dilated and somewhat tortuous. This explains the roentgenographic appearance of ectatic bronchi demonstrated with contrast media centrally since there is no filling possible toward the involved periphery. It also makes understandable the normal behavior of these uninvolved bronchi in the two phases of respiration, i.e., dilating and elongating in inspiration; shortening and narrowing on expiration. In certain instances in which a major bronchus is involved by specific tuberculous inflammation or ulceration, stenosis results. The striking finding here is marked narrowing of the lumen associated with distal dilatation. This is readily demonstrated at bronchography (figure 19), especially when a watery medium is used (figure 20) so that it may pass through the stricture. The roentgenograms of the injected lung specimens are not unlike those seen in nontuberculous cases. The pulmonary arterial pattern is intact (figure 21) except where there are small foci of tuberculous parenchymal disease showing the characteristic obliterative pattern of tuberculosis. The dilated bronchi, however, run to the margin of the lung (figure 22). On the other hand, the histopathologic study of these dilated bronchi distal to the stenosis shows no involvement as opposed to the extensive changes in the bronchi in nontuberculous cases. There is little change in the lung parenchyma beyond collapse of alveoli except when there are small foci of tuberculous disease. A very similar set of findings is noted in the presence of lymph node obstruction with local inflammatory reaction of the bronchus at the hilum producing obstruction (figures 23, 24, 25, and 26).

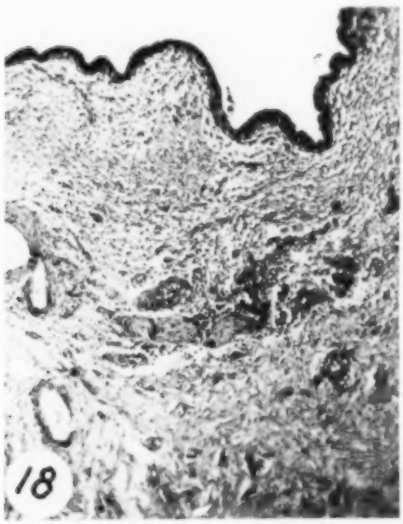
A point of consideration in the pathogenesis of nontuberculous bronchiectasis is the question of congenital or developmental defect. This is considered when in the histopathologic findings irregular patterns of lung structure are noted sugges-

FIG. 15. Case 10. Nontuberculous bronchiectasis; gross appearance. The cylindrically dilated bronchi, coursing through relatively normal appearing pulmonary tissue, are readily seen. Note that the ectasia extends far toward the periphery.

FIG. 16. Case 10. Nontuberculous bronchiectasis. The intact, slightly hyperplastic epithelial lining of the bronchus is at the top. The wall of the bronchus is greatly thickened by dense inflammatory infiltration consisting chiefly of lymphocytes. The musculature of the wall is irregular in distribution, several smooth muscle bundles being seen in the midzone of the figure immediately beneath the mucosa. In the center of the field is an irregular cartilagenous plate, apparently undergoing erosion. (× 100)

FIG. 17. Case 9. Photograph of tuberculous left lung removed at operation. The upper lobe is above and the lower lobe is below. Two cavities are to be seen in the upper lobe, with a trabecula crossing the more lateral one. Between the two cavities a dilated tortuous bronchus is seen. The walls of the hilar bronchi are thickened, but their lumens are of essentially normal size. Hilar vessels, several of which may be seen between the main lobar bronchi, also show thickening of their walls but essentially normal size. Smaller bronchi and vessels are effaced in the areas of scarring or caseation which have almost completely replaced the alveolar structure throughout both lobes.

FIG. 18. Case 9. Photomicrograph of the wall of one of the bronchi showing dilatation and serration of the lining. Note that the mucosa is intact. There is moderate lymphocyte infiltration beneath the mucosa. A portion of the wide area of diffuse collagen deposition is shown, through which the bronchus courses. All evidence of bronchioles, alveolar ducts, and alveoli are effaced. (× 100)



FIGS. 15-18

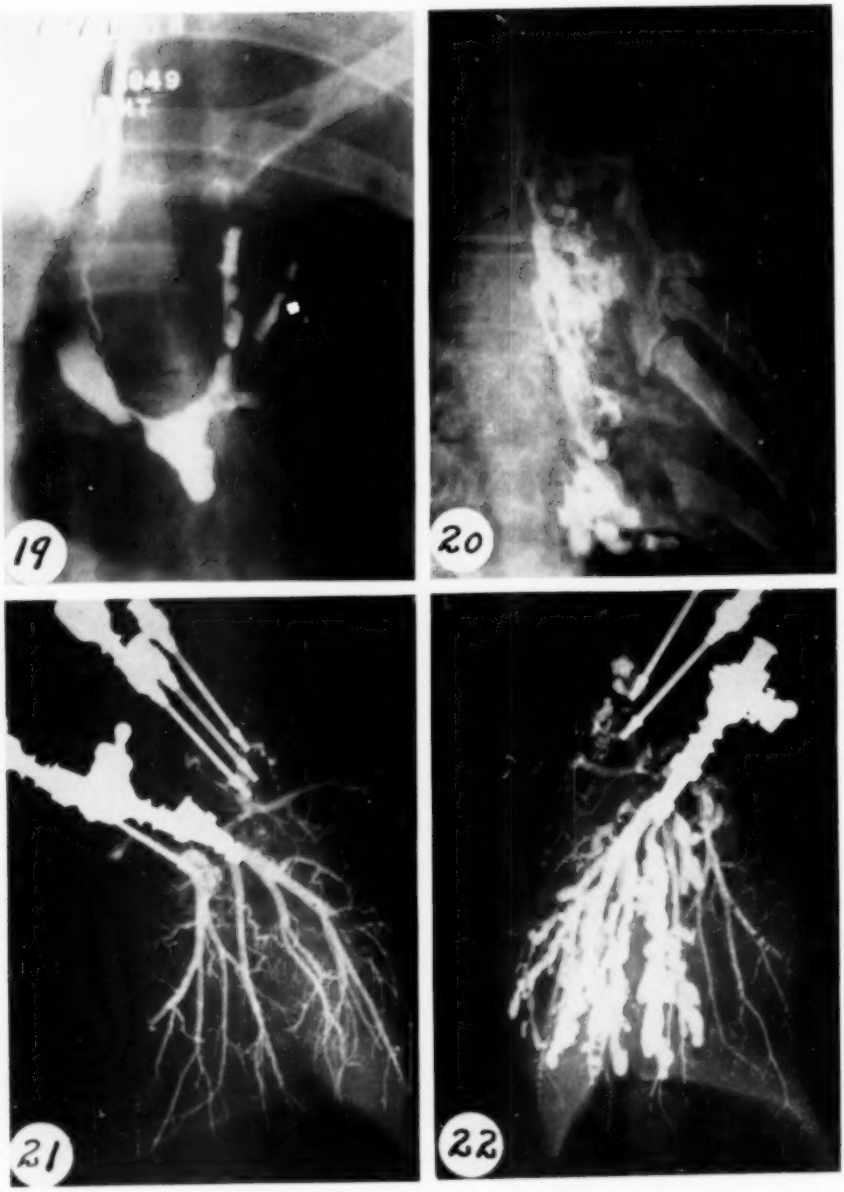
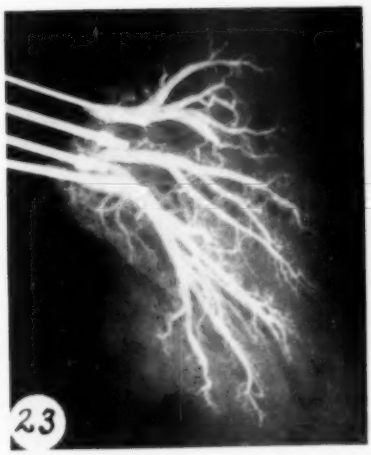


FIG. 19. Case 11. Bronchogram in presence of tuberculous fibrostenosis showing marked narrowing. Oil contrast medium enters other bronchi with difficulty.

FIG. 20. Case 11. Post-thoracoplasty bronchogram using watery contrast medium showing marked stenosis with distal dilatation to periphery.

FIG. 21. Case 11. Lower lobe of surgically removed specimen with pulmonary artery injection mostly normal except for absence of branching at site of tuberculous foci.

FIG. 22. Case 11. Same specimen with segmental bronchial injection distal to stenosis. Note similarity to pattern in life and to nontuberculous disease with dilated bronchi.



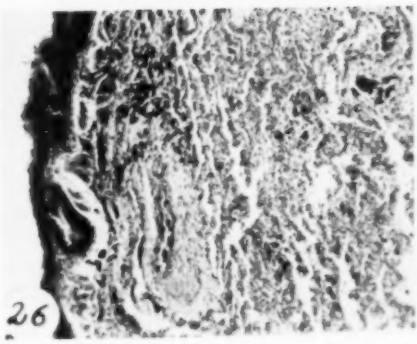
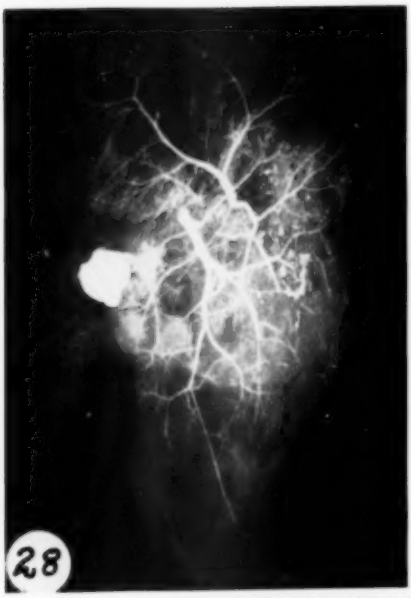


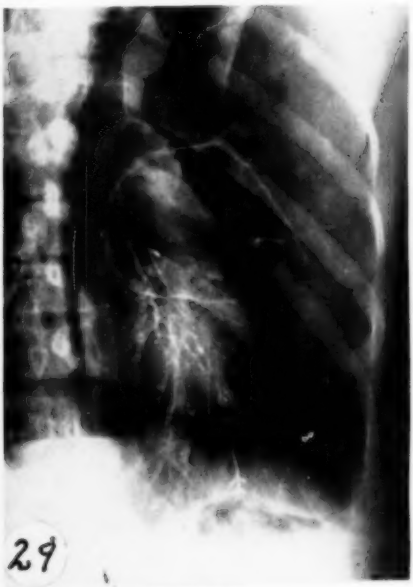
FIG. 23. Case 12. Pulmonary artery injection of surgically removed middle lobe for stenosis of its bronchus and focal tuberculosis. Pattern relatively normal except at scattered foci of tuberculosis.

FIG. 24. Case 12. Same with bronchi injected distal to stenosis showing dilated bronchi going to periphery as in nontuberculous disease.

FIG. 25. Case 12. Post-stenotic distal bronchiectasis; gross appearance. The specimen has been injected with a gelatin-bismuth mass which has been fixed *in situ*. In the bronchi the mass is white, while it is dyed pink in the pulmonary arteries. Note the irregular, more or less cylindrical, dilatations of the bronchi extending far to the periphery. In contrast, the vessels are small, regular in outline, and taper uniformly. The pulmonary tissue is generally collapsed. A few encapsulated caseous foci are present, especially beneath the lateral pleura, but the involvement is not of sufficient extent nor is it properly located to produce the bronchial alterations.

FIG. 26. Case 12. Post-stenotic bronchiectasis. The intact epithelial lining of the bronchus is at the left. The wall of the bronchus is thin and shows only slight lymphocytic infiltration. A continuous layer of smooth muscle bundle is present beneath the mucosa. The adjacent pulmonary tissue is collapsed and shows slight lymphocytic infiltration. The appearance suggests that, if properly aerated, the alveoli could expand. (× 100)





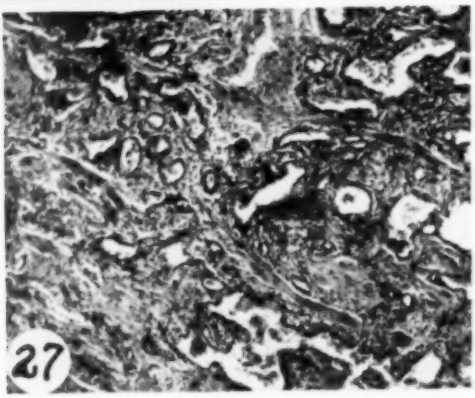


FIG. 27. Case 13. An area of lung tissue several millimeters from any bronchus. The irregular spaces are alveoli lined by cuboidal epithelium. In the thick alveolar septa, there are numerous dense bundles of smooth muscle fibers which have an entirely normal appearance except for their location. The structure at the upper margin is a small artery. (× 100)

FIG. 28. Case 14. Pulmonary artery injection of surgically removed left upper lobe showing intact but sparse pattern compared with normal, and contrasted to tuberculosis.

FIG. 29. Case 14. Roentgenogram showing cystic upper lobe and normal bronchogram of lower lobe.

tive of incomplete development (figure 27). On the basis of a limited number of cases, there is some suggestion that the injection method of study might significantly contribute to the answer to this facet of the problem.

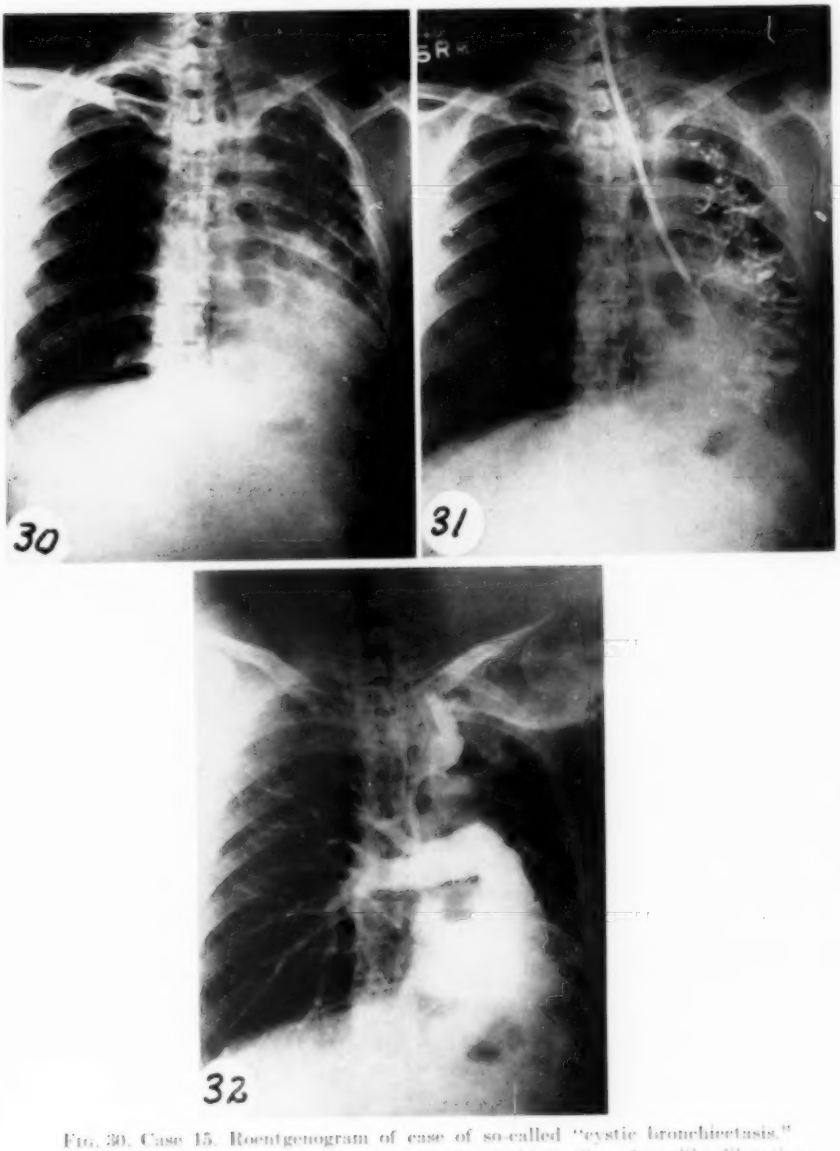


FIG. 30. Case 15. Roentgenogram of case of so-called "cystic bronchiectasis."
FIG. 31. Case 15. Same as above showing bronchographic outline of cystlike dilatations.
FIG. 32. Case 15. Angiogram showing good pattern of right pulmonary arterial system and no evidence of filling on the left side.

The pattern of the injected pulmonary artery in a removed cystic lobe (figures 28 and 29) appears smaller in caliber and there are fewer branches. This pattern

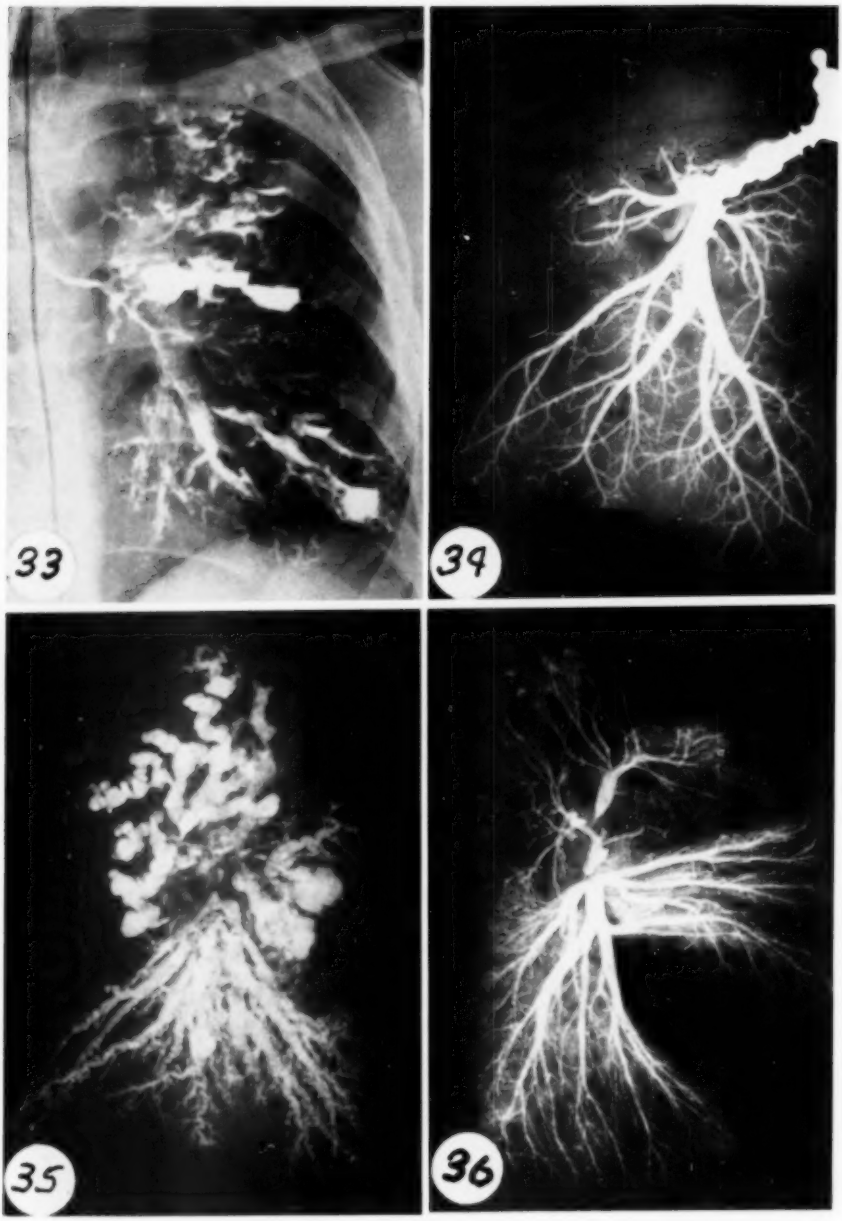


FIG. 33. Case 16. Bronchogram in patient with sputum positive for *M. tuberculosis* showing easily filled cystic dilatations similar to those seen in figure 29.

FIG. 34. Case 16. Injection of pulmonary artery of removed left lung shown above. There is minimal filling in the upper lobe and a relatively normal pattern in lower lobe except in the region of unclosed tuberculous cavity.

FIG. 35. Case 16. The injected bronchi appear dilated rather than cystic as in figure 33. This change is believed to be secondary to prior thoracoplasty collapse.

FIG. 36. Case 17. Injection of pulmonary artery in removed right lung for cystic bronchiectasis showing diminished pattern in upper lobe and normal pattern in middle and lower lobes.

is in contrast to the normal lung, the bronchiectatic lung, and the tuberculous lung. On examination, the lobe had the characteristics of a developmental defect (3). The roentgenograms of a case of cystic bronchiectasis (figure 30), obtained through the courtesy of Dr. C. Dotter of New York City, show in the bronchogram (figure 31) small semilunar shadows scattered throughout. In the angiogram (figure 32), good filling is noted in the normal right lung, but very little evidence of pulmonary artery is seen on the left. In another case (figure 33) with identical bronchogram pattern as above, but with sputum containing tubercle bacilli, the lung was ultimately removed after thoracoplasty failure. Injection of the pulmonary artery (figure 34) shows very minimal filling in the upper lobe area. A normal pattern is seen in the lower lobe except in the region of a small unclosed tuberculous cavity, in which the usual obliterative findings are noted. The injected bronchi appear markedly dilated in the region of the abnormal pulmonary arterial pattern (figure 35). On histologic examination, there was poorly developed lung but no evidence of any previous tuberculous infection except in the lower lobe. Another case, seen through the courtesy of Drs. Allan Stranahan and Walter Gobbel, of Albany, New York, showed evidence of cystic bronchiectasis in the upper lobe. For technical reasons, the entire lung was removed. The injection study of the pulmonary artery (figure 36) shows a diminished pattern in the upper lobe, and the middle and lower lobe patterns are distinctly normal.

Such material suggests that there is a possibility of distinguishing congenital or developmental defects from acquired changes by studying the pulmonary arterial system on direct injection of the specimen and by angiography. While failure of development of the lung may be on a congenital basis, it must be recalled that the lung is known to continue its postnatal growth up through middle childhood (4). Should a severe infection be superimposed during this growing phase, perhaps certain irreversible changes or arrest of development might occur. These changes would be carried through later life and might well account for the reported bizarre pattern seen in some cases of nontuberculous bronchiectasis.

DISCUSSION

Some means of differentiating types of bronchiectasis would be helpful, not only from an etiologic standpoint, but would aid in clarifying some of the inconstant findings. The clinician uses the term in cases in which there is excessive expectoration of purulent, foul sputum, usually beginning in childhood and persisting in later life. Occasionally, a previously asymptomatic adult develops the same symptoms following a severe lower respiratory illness. The demonstration of dilated bronchi with contrast medium is the roentgenographic means of making a diagnosis of bronchiectasis, whereas the pathologist looks for certain histopathologic changes (5). Exceptions to the common form of bronchiectasis are seen by the clinician, the radiologist, and the pathologist. Other variables have been added recently when physiologic studies were made (6). In another study of 40 cases of bronchiectasis (7), substantiated by iodized oil, a considerable variation in the physiologic status of the respiratory apparatus was observed. The degree to which the arterial hemoglobin was saturated was normal in some but moder-

ately subnormal in others during physical exercise. The possible relationship between pulmonary arterial patency and physiologic observations was indicated in a previous report (8).

The demonstration of dilated bronchi with contrast media is only one of the structural alterations in bronchiectasis. There are multiple etiologic factors which give rise to this secondary manifestation of pulmonary change. In uncomplicated atelectasis, dilated bronchi have been demonstrable and, when reaeration of the lung was established, this finding disappeared (9). Reversible bronchiectasis has been noted also, associated with certain transient lower respiratory disease (10). Neither of these two types of case was available for this study. In pulmonary tuberculosis, dilated bronchi are seen in the inner two-thirds secondary to surrounding parenchymal disease, whereas these major tubes are themselves uninvolved. On the other hand, when the main bronchus is involved by specific tuberculous infection, there is evidence of stenosis with distal dilatation secondary to the stricture. There is associated collapsed, but not necessarily diseased, lung. This same phenomenon must explain lymph node encroachment at the hilum in certain cases of demonstrated ectasia unaccompanied by symptoms since infection need not be present (11, 12). In nontuberculous disease the tubular system is extensively involved, either by direct infection or superimposed upon a collapsed lung segment. Here the dilated bronchi extend to the pleural margin of the lung, as seen at bronchography, in the injected specimen, and by direct examination. Evidence that this was once a normal lung is provided by the demonstration of intact pulmonary arterial system. These are contrary findings to those noted in pulmonary tuberculosis. In cases of what has been considered to be developmental defects, other findings are noted. The bronchial pattern is usually of the cystic type, and the pulmonary arterial pattern is poorly developed rather than obliterated by infection as in tuberculosis, or uninvolved as in nontuberculous disease. These findings help toward a better understanding of the clinical course, roentgenographic observations, and pathologic variables. It is clear that bronchiectasis, as evidenced by the demonstration of dilated bronchi, may be unaccompanied by symptoms. The change may be secondary to lymph node or other bronchial encroachment without parenchymal infection, or may be secondary to old inactive pulmonary tuberculosis. The usual symptoms of classical bronchiectasis may be present because of severe infection causing irreversible changes in the bronchi. Transient symptoms may disappear because of relief of the obstruction, with recovery from the infection unaccompanied by damage to the bronchi.

The histopathologic variables are understandable on a simple etiologic basis:

(*1*) obstruction with distal dilatation, (*2*) nontuberculous specific destructive changes, (*3*) tuberculous parenchymal or local disease, and (*4*) developmental defects with or without infection.

Regarding the inconstant physiologic findings, there may be decrease in both ventilation and circulation as in tuberculosis; decrease to absence of ventilation, but perfusion being possible because of an intact pulmonary arterial system; or large dead space as in cystic changes with a greatly decreased vascular bed.

SUMMARY

The material here presented makes it possible to separate bronchiectasis according to etiologic factors by recognizing certain fundamental differences.

Segmental lobar location in nontuberculous bronchiectasis is in the basal and posterior portions of the lung. In tuberculosis, localization is apical and posterior with respect to any involved lobe or lobes.

The bronchographic patterns show extension of the ectasia to the periphery in nontuberculous disease and limitation to the medial two-thirds in tuberculosis.

Bronchial caliber change in inspiration and expiration is seen in tuberculosis and is practically absent in nontuberculous bronchograms.

Lung specimens injected with contrast medium reproduce the bronchogram pattern but reveal differences in the pulmonary arterial pattern. In nontuberculous disease there is normal filling in contrast to paucity of vascular demonstration in tuberculosis. In lung tissue which shows developmental defects, the pulmonary arterial pattern appears poorly developed and unlike the other two.

The histopathology reveals, among other things, the extensive tubular system damage in nontuberculous disease in contrast to parenchymal involvement in tuberculosis.

SUMARIO

La Bronquiectasia: Estudio Comparativo

Los datos aquí presentados permiten separar la bronquiectasia de acuerdo con los factores etiológicos mediante el reconocimiento de ciertas diferencias fundamentales.

En la bronquiectasia no tuberculosa, la localización en un segmento lobular corresponde a las porciones basal y posterior del pulmón. En la tuberculosa, la localización es en los vértices y posterior con respecto al lóbulo o lóbulos afectados.

Los patrones broncográficos revelan difusión de la ectasia a la periferia en las afecciones no tuberculosas y limitación a los tercios del medio en la tuberculosis.

En la tuberculosis, obsérvanse alteraciones del calibre bronquial a la inspiración y la expiración que prácticamente no existen en los broncogramas no tuberculosos.

Los ejemplares pulmonares invectados con medios de contraste reproducen los patrones broncográficos, pero revelan diferencias en el patrón arteriopulmonar. En las afecciones no tuberculosas, hay henchimiento normal en contraposición a la escasa visualización vascular en la tuberculosis. En el tejido pulmonar que revela anomalías del desarrollo, el patrón de las arterias pulmonares parece estar mal desarrollado y ser distinto de los otros dos.

El estudio histopatológico revela, entre otras cosas, extensas lesiones del aparato tubular en las afecciones no tuberculosas, en contraposición a la invasión parenquimática observada en la tuberculosis.

RESUME

Bronchiectasie: Etude comparative

Les informations présentées permettent d'établir une classification des bronchiectasies selon les facteurs étiologiques en considérant certaines différences fondamentales.

La localisation segmentaire lobaire de la bronchiectasie non tuberculeuse est la région basale et postérieure du poumon. Dans la tuberculose, la localisation est apicale et postérieure dans un ou dans chacun des lobes intéressés.

L'aspect bronchographique montre l'extension de l'ectasie vers la périphérie dans les affections non tuberculeuses et limitation aux deux tiers moyens dans la tuberculose.

Les modifications du calibre bronchique dans l'inspiration et dans l'expiration, qui s'observent dans la tuberculose, sont pratiquement absentes des bronchogrammes non tuberculeux.

Les coupes de poumons injectés avec une substance opaque reproduisent l'image du bronchogramme, mais révèlent des différences dans l'aspect artériel pulmonaire. Dans les affections non tuberculeuses le remplissage est normal, par contraste avec la rareté des manifestations vasculaires dans la tuberculose. Dans les tissus pulmonaires où apparaissant des défauts de développement, le type artériel pulmonaire apparait insuffisamment développé et sans ressemblance avec l'aspect des deux autres types.

L'histo pathologie révèle, entre autres choses, des lésions étendues de l'arbre bronchique dans les affections non tuberculeuses, par contraste avec l'altération du parenchyme dans la tuberculose.

Acknowledgments

The radiographic illustrations were prepared by Anna M. Sanlow, Senior X-ray Technician, Ray Brook State Tuberculosis Hospital, Ray Brook, New York.

The pathologic illustrations were prepared by Edward Gockeler, Photographer, Saranac Laboratory, Saranac Lake, New York.

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TRANSIENT UNDIAGNOSED INTRATHORACIC LYMPHADENOPATHY IN APPARENTLY HEALTHY PERSONS[1]

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(Received for publication June 23, 1952)

INTRODUCTION

Intrathoracic lymphadenopathy is frequently discovered in apparently healthy persons by means of routine chest roentgenography. It is well recognized that such a finding may represent a manifestation of either a chronic disease, e.g., tuberculosis, sarcoidosis (1, 2), lymphoma (3); or an acute disease, such as infectious mononucleosis (4) or erythema nodosum (5). It is not widely known, however, that intrathoracic lymph node involvement in asymptomatic patients may be a transient benign condition, unassociated with a preceding illness or any other visceral involvement.

In recent years, the writers have encountered a number of such cases in which a diagnosis was never established. In spite of this shortcoming, it was believed to be worth while to report this group of patients in order to alert physicians to the possibility of spontaneous regression in a person with unexplained silent intrathoracic lymph node enlargement.

It is to be emphasized that all of the patients in this series were asymptomatic throughout the period of observation and were, therefore, reluctant to undergo many of the recommended procedures which obviously were essential to establish a diagnosis. In such circumstances, the only reason for reporting this group of cases is simply to demonstrate the fact that substantial transient enlargement of intrathoracic lymph nodes can occur without associated symptoms.

It should be particularly emphasized that there is no implication that the present findings represent a distinct disease entity or that intrathoracic lymphadenopathy per se is a trivial finding which requires no serious diagnostic measures.

SELECTION OF MATERIAL

A large volume of material available from the twenty-three chest clinics and the survey units of the Bureau of Tuberculosis was screened for asymptomatic patients with obvious intrathoracic lymphadenopathy discovered on a survey or routine chest roentgenogram. Patients who had spontaneous regression of the nodes and no evidence of pulmonary or other visceral involvement throughout the period of observation form the basis of the present report. These criteria were fulfilled in 20 cases.

The clinical observations in all instances were limited to those which could be carried out in a chest clinic without jeopardizing the cooperation of the patients. The difficulty of conducting intensive clinic investigations in a group of asymptomatic patients is well known to those who have attempted follow-up

[1] From the Bureau of Tuberculosis, New York City Department of Health, 125 Worth Street, New York, New York.

studies on survey cases. It was necessary to be content, therefore, with the following minimal observations: history, including details of occupational and geographical background; physical examination; serial chest roentgenograms, including both conventional and lateral projections; roentgenograms of the hands; tuberculin tests; and serologic tests for syphilis.

None of the patients with palpable peripheral lymph nodes submitted to a biopsy. Two patients with unilateral hilar involvement refused to undergo a recommended exploratory thoracotomy. In none of the cases was a definite diagnosis established.

The age, sex, race, and period of observation for each of the patients are listed in table 1. The period of observation was between five and nine and one-half years in 10 patients and between one and three and one-half years in 10, with a mean observation period of five years.

All patients had been residents of New York City for a long time without significant occupational exposure or allergic disposition. None of the patients had knowledge of a preceding illness or recent exposure to an infectious disease.

OBSERVATIONS

At Time of Discovery

Symptoms and physical findings: All of the patients were asymptomatic and afebrile. In 6, slightly enlarged peripheral lymph nodes were present. There were no other significant positive physical findings.

Laboratory findings: Erythrocyte, leukocyte, and differential cell counts, done in 10 patients, were within normal limits. Chemical blood determinations and erythrocyte sedimentation rates, obtained in only 4 instances, were normal. All serologic tests for syphilis were negative.

The cutaneous reactions to *tuberculin* are noted in table 1. Kveim tests, done in 3 persons, and histoplasmin tests (1:100 dilution), done in 4, were negative.

Roentgenographic findings: In all of the cases, striking enlargement of some intrathoracic lymph nodes was noted. All but 4 of the patients had obvious bilateral involvement, 2 had unilateral involvement, and 2 with predominantly right-sided disease also had slight lymph node enlargement at the left hilum.

The variety of findings noted in the chest roentgenograms is apparent from a review of figures 1 to 8. The variation in location and size of the involved nodes are noted in table 1.

Eight patients had normal chest films which had been obtained three months to five years prior to discovery of the lymphadenopathy.

Roentgenographic studies of the hands were normal in all patients.

Follow-up Observations

All patients had an asymptomatic, afebrile, and uneventful course. Peripheral lymphadenopathy, whenever present, receded simultaneously with the enlarged intrathoracic lymph nodes.

In only 11 patients were serial roentgenograms taken with a sufficient degree of frequency to indicate, even roughly, the rate of regression of the lymphad-

TABLE 1

OBSERVATIONS ON 19 CASES OF TRANSIENT INTRATHORACIC LYMPHADENOPATHY

	PATIENT	AGE	SEX	RACE	DATE OF DISCOVERY	TUBERCULIN REACTION AT DISCOVERY		ROENTGENOGRAPHIC FINDINGS AT DISCOVERY*				INTERVAL FROM DISCOVERY TO FIRST NORMAL ROENTGENOGRAM	PERIOD OF OBSERVATION	ROENTGENOGRAPHIC REPRODUCTIONS
								Hilar		Paratracheal				
						0.01 mg. O.T.	1 mg. O.T.	Right	Left	Right	Left			
												Months		
1.	R. E.	26	F	W	October 1941	Negative	Positive	+	++	+	0	4	9½ years	
2.	J. Ro.	25	M	W	January 1942	Negative	Positive	++	++	+	0	24†	9½ years	Figure 1
3.	T. G.	33	M	W	March 1942	Positive		+++	++	0	0	9	9 years	Figure 2
4.	E. B.	24	M	W	August 1942	Negative	Negative	++	++	+	0	18†	8 years	
5.	T. T.	23	M	W	November 1942	Negative	Negative	++	++	0	0	5	9 years	
6.	M. M.	19	M	W	March 1943	Negative	Negative	++	++	+	0	10†	7 years	
7.	F. K.	30	M	W	April 1943	Positive		++	+	0	0	9†	5½ years	
8.	H. F.	22	M	W	February 1944	Negative	Negative	++	++	++	0	12†	5 years	Figure 3
9.	M. T.	22	F	N	May 1946	Negative	Negative	+++	+++	+	Calcification	10†	5½ years	Figure 4
10.	F. H.	22	F	N	February 1947	Negative	Negative	+++	+++	++	0	12†	5 years	
11.	W. L.	24	M	W	September 1948	Negative	Negative	++	++	+	0	10†	3½ years	Figure 5
12.	C. R.	29	F	N	April 1949	Positive		++	++	+	+	6	2½ years	
13.	J. Ri.	31	M	W	August 1949	Positive		++	++	+	+	8	2½ years	
14.	M. L.	25	F	N	May 1950	Negative	Positive	++	++	0	0	16†	2 years	Figure 6
15.	L. S.	26	F	W	July 1950	Negative	Not done	++	0	0	0	4	20 months	
16.	C. L.	22	M	N	February 1951	Negative	Negative	++	++	0	0	7	14 months	
17.	G. N.	23	M	W	March 1951	Negative	Negative	++	++	0	0	6	13 months	
18.	D. J. C.	21	M	W	April 1951	Negative	Negative	++	+	0	0	4	12 months	Figure 7
19.	A. H.	52	F	W	May 1951	Negative	Positive	++	0	0	0	7	12 months	Figure 8
20.	D. F.	29	F	W	June 1951	Not done		++	++	0	0	2½	12 months	

* Definition of descriptive terms and symbols:

Location:

Hilar: adjacent to or below root structures

Paratracheal: above root structures

Size of involved nodes:

\+ slightly enlarged

++ moderately enlarged

+++ markedly enlarged

† No intervening roentgenograms

Addendum: An additional period of four months since submitting the paper revealed no changes in the clinical status of the patients.

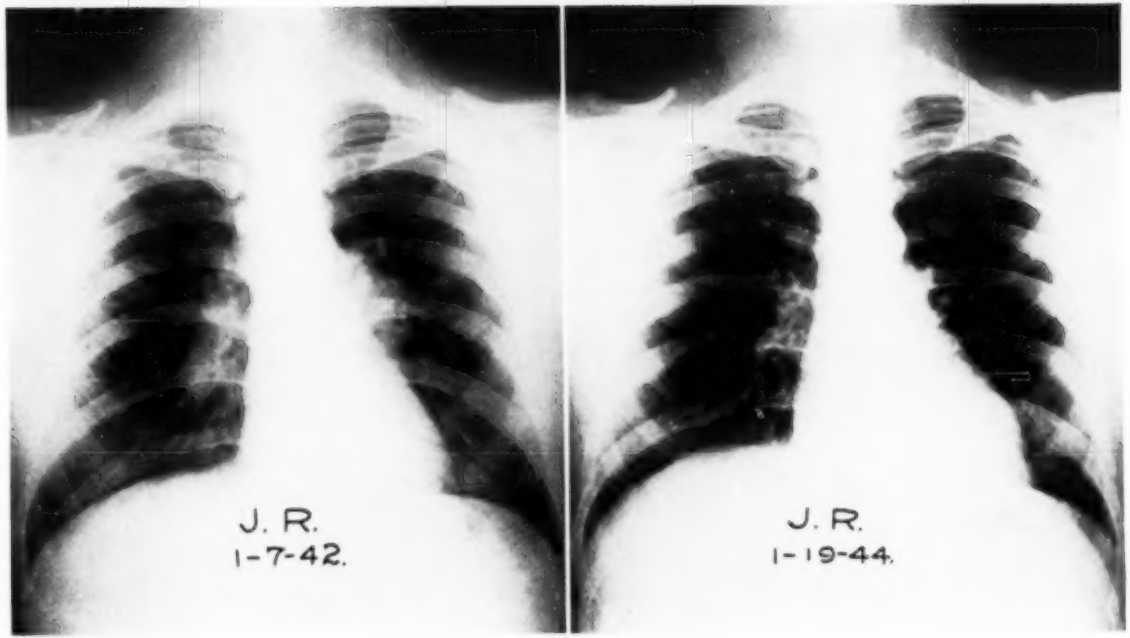

FIG. 1. *Case 2*

(Left) Moderately enlarged hilar and slightly enlarged paratracheal nodes.
(Right) Complete regression two years later.

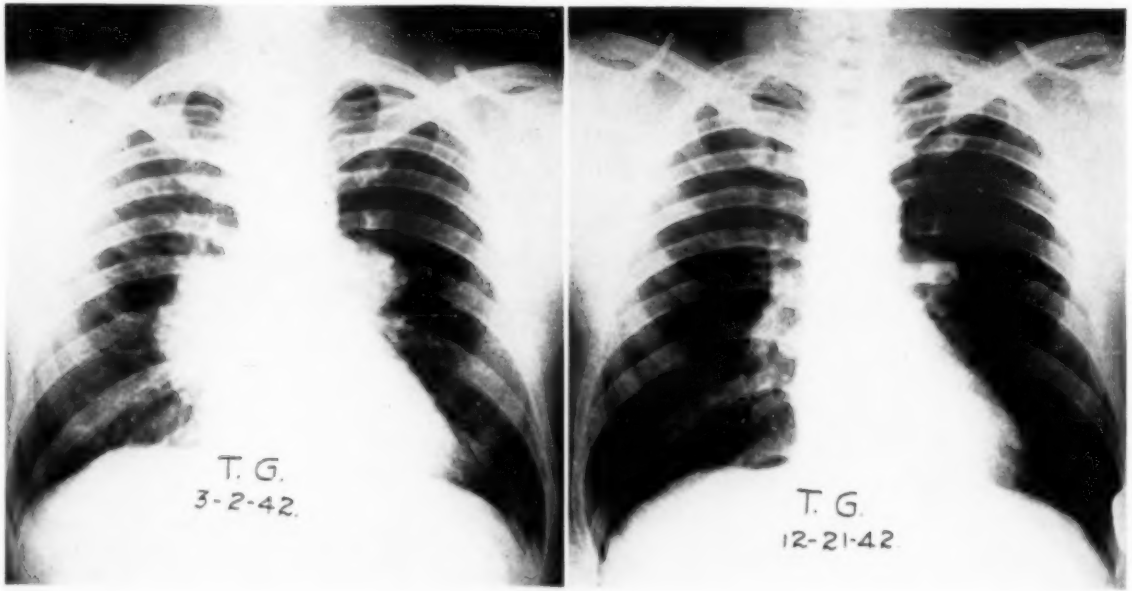

FIG. 2. *Case 3.*

(Left) Markedly enlarged right and moderately enlarged left hilar nodes.
(Right) Complete regression nine months later.

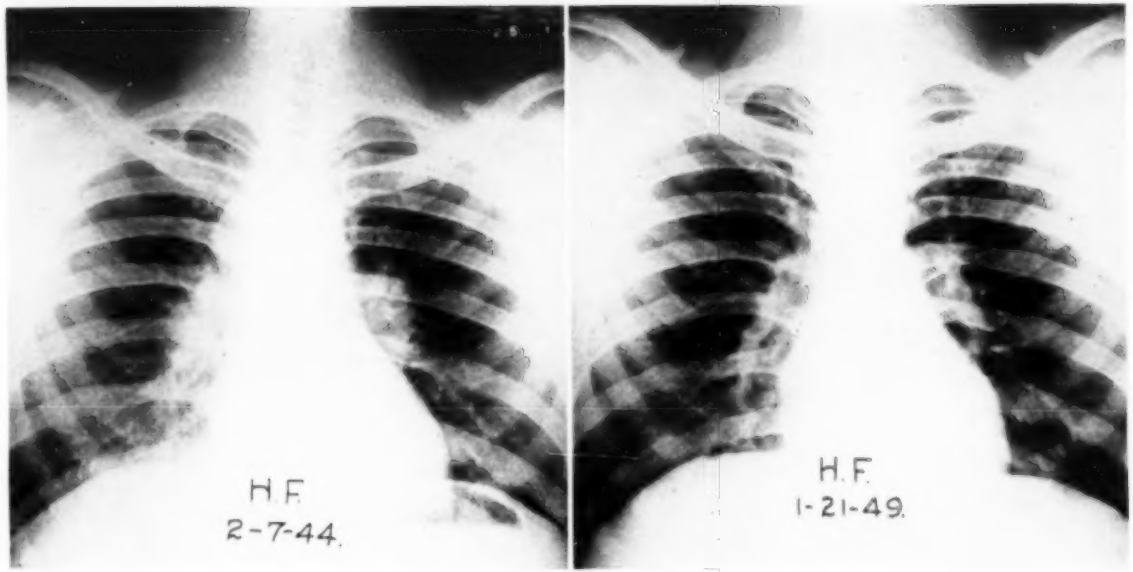

FIG. 3. *Case 8*

(Left) Moderately enlarged hilar and right paratracheal nodes.
(Right) Normal chest film taken five years later and four years after complete regression was first noted.

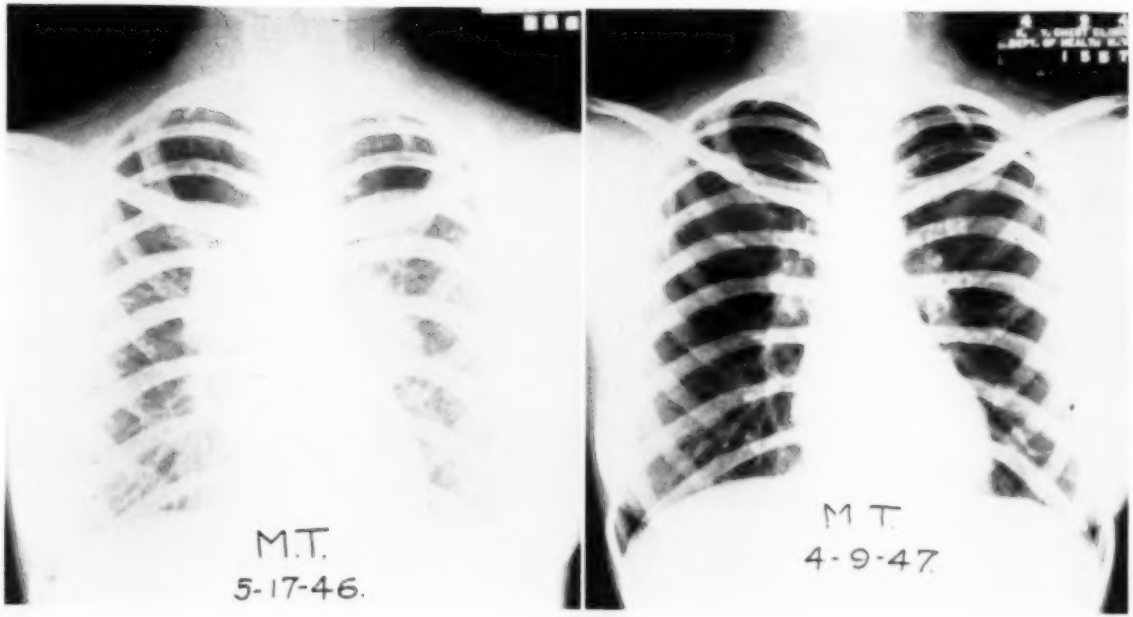

FIG. 3. *Case 9*

(Left) Markedly enlarged hilar nodes; calcification in left paratracheal area. Tuberculin test negative.
(Right) Complete regression ten and one-half months later. Tuberculin test now positive.

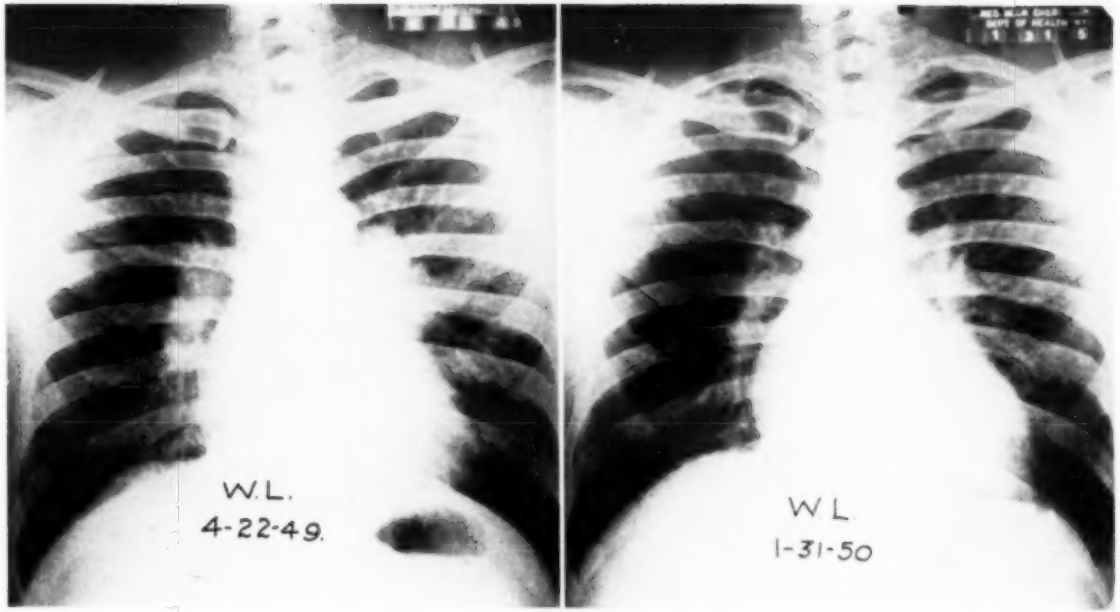

FIG. 5. *Case 11*

(Left) Moderately enlarged hilar and slightly enlarged paratracheal nodes.
(Right) Complete regression nine months later. No clinical evidence of heart disease; blood pressure normal.

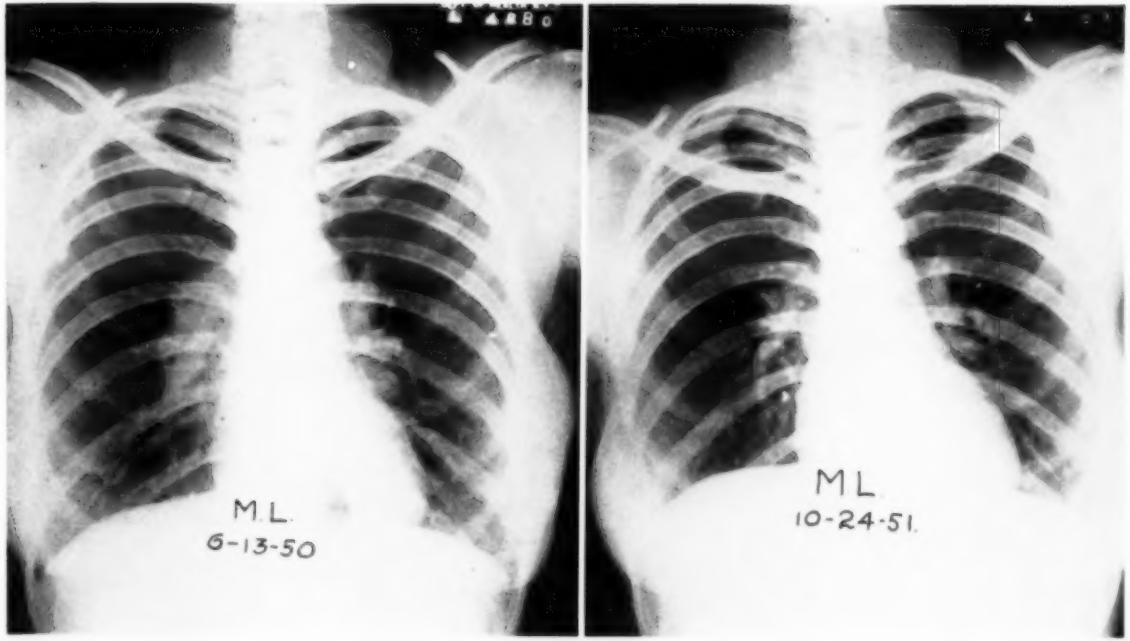

FIG. 6. *Case 14.*

(Left) Moderately enlarged hilar nodes.
(Right) Complete regression sixteen months later.

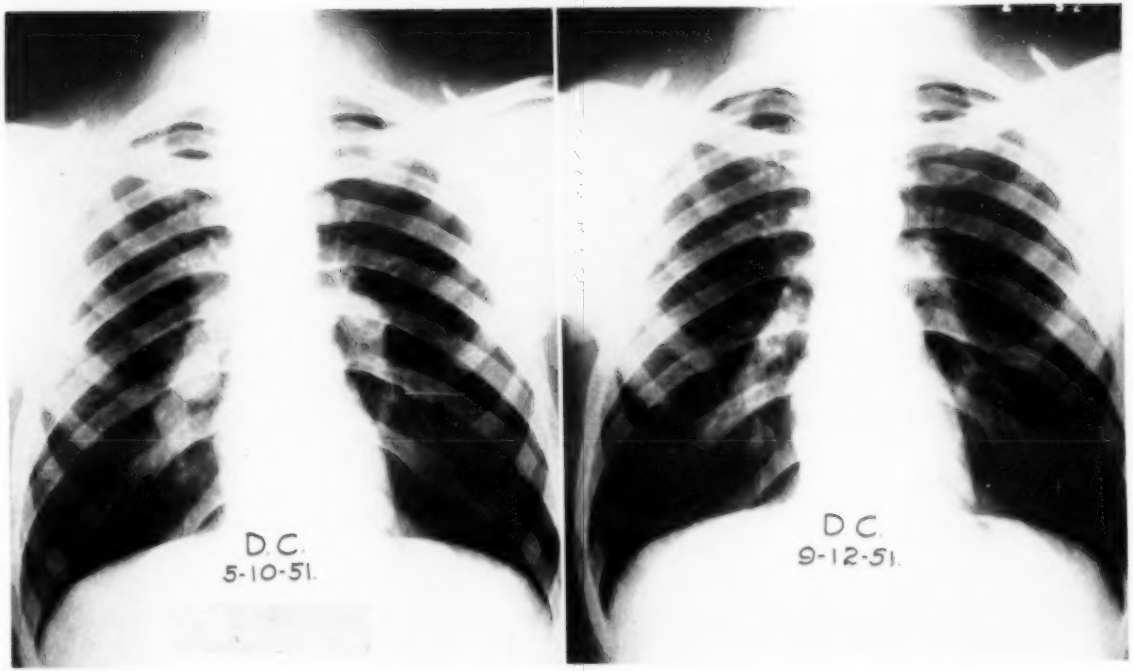

FIG. 7. *Case 18*

(Left) Masses of nodes adjacent to right hilum; slightly enlarged left hilar nodes.
(Right) Complete regression four months later.

FIG. 8. *Case 19*

(Left) Mass at right hilum, located in middle mediastinum on lateral projection.
(Right) Normal chest film nine and one-half months later and two and one-half months after complete regression.

enopathy (table 1). The regression was a gradual one in all instances and occurred within an average period of six months. In one case (W. L.), progression in the size of the involved nodes was noted one month after discovery, with subsequent disappearance within the next nine months. Calcification at the site of the enlarged nodes was not observed in any of the patients. In no instance was a recurrence of any lymphadenopathy noted once regression had been completed.

In 3 patients, a previously negative tuberculin reaction became positive within two years after discovery. The remaining patients, when retested, showed no change from their original reaction to tuberculoprotein.

DISCUSSION

More thorough investigations than were possible with the present material are necessary to determine to what extent cases such as those reported here are merely variants of established diseases, such as sarcoidosis, tuberculosis, infectious mononucleosis, erythema nodosum, or any of the mycoses, or actually represent as yet unrecognized conditions.

Nevertheless, whatever may be the underlying nature of the involved nodes, in the writers' experience, transient benign intrathoracic lymph node enlargement is one of the most frequent forms of lymphadenopathy encountered in the course of routine chest roentgenographic examination of apparently healthy adults. For this reason, it is pertinent to discuss some of the diagnostic procedures employed in patients with accidentally discovered intrathoracic lymph node enlargement.

Unquestionably, the finding of intrathoracic lymphadenopathy calls for the most intensive clinical investigations (6), including biopsy of peripheral lymph nodes, if possible, and the use of the Kveim reaction (7). Frequently, however, these studies fail to establish a definite diagnosis. In such instances, when the disease is limited to one side of the mediastinum, the present writers advocate the use of prompt surgical exploration, not alone for diagnostic purposes, but for the opportunity thus afforded to excise a resectable carcinoma or localized lymphoma (3, 8). When there is bilateral involvement, on the other hand, an exploratory thoracotomy is only of diagnostic help. In such circumstances, surgical exploration without too much delay would still be considered the indicated procedure by those physicians who stress early, intensive radiation therapy for some of the lymphomas (3, 8). For those who believe that there is little risk in delaying radiation in such instances, close observation of asymptomatic patients with undiagnosed intrathoracic lymphadenopathy offers the opportunity of recognizing spontaneous regression or other clinical developments which may help to establish a definite diagnosis.

In any event, it is believed that, in asymptomatic patients with intrathoracic lymphadenopathy, there is little justification at the present time for the use of radiation therapy in the absence of a histologic diagnosis. With the low mortality rates of present-day exploratory thoracotomy, a so-called "diagnostic" trial of radiation, frequently employed in the past, is now best avoided. The results of "diagnostic" radiation are of no value in distinguishing between the various

forms of benign and malignant intrathoracic lymph node enlargement, each of which requires a different therapeutic approach (8). In addition, this procedure, on occasion, may coincide with—and thus mask—spontaneous regression. As a consequence, a serious prognosis is falsely suggested, with resulting unnecessary hardship on patient and family.

It would be well also to keep in mind the possibility of spontaneous regression as noted in this group of cases when evaluating the therapeutic results of cortisone, corticotropin (ACTH), or antimicrobial agents, which are now occasionally employed in patients with undiagnosed intrathoracic lymphadenopathy.

SUMMARY

In 20 asymptomatic persons, survey chest roentgenograms revealed the presence of obvious intrathoracic lymphadenopathy of an indeterminate nature which subsequently underwent spontaneous regression. With one exception, the patients were between nineteen and thirty-one years of age; 15 were white and 5 were Negro. Ten patients had negative cutaneous reactions to 1 mg. of OT. The hilar area was affected in all instances. Eighteen patients had bilateral and 2 had unilateral involvement; paratracheal node enlargement occurred in 7 patients. In 11 patients who could be followed at sufficiently frequent intervals, complete disappearance of the lymphatic enlargement was observed within two and one-half to nine months. All of the patients, observed for a mean period of five years, have remained in good health without evidence of recurrence or other visceral involvement.

SUMARIO

Linfadenopatía Intratorácica Transitoria no Diagnosticada en Personas Aparentemente Sanas

En 20 personas asintomáticas, radiografías torácicas tomadas en encuestas revelaron la presencia de manifiesta linfadenopatía intratorácica de naturaleza indeterminada que luego experimentó regresión espontánea. Con una excepción, los sujetos tenían de 19 a 31 años de edad, siendo 15 blancos y 5 negros. Diez acusaron cutirreacciones negativas a 1 mg. de TA. En todos estaba afectada la región hiliar: en 18 bilateralmente y en 2 unilateralmente, habiendo linfadenitis paratraqueal en 7. En 11 enfermos, que pudieron ser observados a plazos suficientemente frecuentes, se notó despejo total en término de dos y medio a nueve meses. Todos los sujetos, observados durante un promedio de cinco años, han permanecido en buena salud sin signos de recurrencia o de invasión de otros órganos.

RESUME

Adénopathie intra thoracique temporaire non diagnostiquée chez des sujets en bonne santé apparente

Chez 20 individus indemnes de symptômes pathologiques apparents, des radiogrammes périodiques ont révélé l'existence d'une adénopathie évidente, de nature indéterminée, qui a spontanément régressé par la suite. A une exception près, les sujets avaient de 19 à 31 ans, 15 d'entre eux appartenaient à la race blanche, 5 à la race noire. Le tuberculin test avec une dose de 1 mg. de OT a été négatif chez 10 sujets. La zone hilaire était intéressée dans tous les cas l'adénopathie était bilatérale dans 18 cas, unilatérale dans 2 cas l'hypertrophie du ganglion paratrachéal été observée dans 7 cas. Chez 11 individus qui ont pu être surveillés à intervalles suffisamment fréquents, la disparition complète de l'adénopathie s'est manifestée entre deux mois et demi et neuf mois. Tous ces sujets, dont l'observation s'est pour-

suivie pendant une période moyenne de cinq ans, sont demeurés bien portants sans aucun signe de récidive ou d'autre lésion organique.

Acknowledgment

The writers wish to express their thanks to Mr. V. Gill for preparing the roentgenographic reproductions for this report.

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THE CYTOLOGY OF THE TUBERCLE BACILLUS WITH REFERENCE TO MITOCHONDRIA AND NUCLEI[1, 2]

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(Received for publication May 28, 1952)

INTRODUCTION

In living cells of the tubercle bacillus examined in an unstained wet amount with the light microscope, brightly refractile granules may be seen in the cytoplasm. In the phase-contrast microscope, these brightly refractile granules are dark and dense in a clear cytoplasm (1). In addition, a less distinct, irregular central area, denser than the cytoplasm, may be seen.

Mudd and associates (2) published evidence suggesting that these granules found in *Mycobacterium thamnopheos* and *Mycobacterium tuberculosis* var. *hominis* are mitochondria. The present work not only confirms this hypothesis but contributes the additional information that the irregular central areas seen in the phase-contrast microscope correspond to nuclei. These observations are commensurate with those of Knöll and Zapf (3) on the gram-negative bacteria; they, however, refer to the dark granules as cytoplasm.

MATERIALS AND METHODS

The organisms, *M. thamnopheos* and *M. tuberculosis* var. *hominis*, strain H37Rv[4], were used in this study. The organisms were cultivated on 5 per cent glycerol agar with a fresh infusion broth base.

Preparation of impression smears:

Inocula were spread in a thin film on 5 per cent glycerol agar plates and incubated at room temperature for twelve hours for *M. thamnopheos* and at 37°C. for ninety-six hours for human tubercle bacilli.

Blocks of agar were cut out after incubation and the cells were fixed in the vapors of 2 per cent aqueous OsO_4 for one minute.

The cells were inverted onto albumin-coated[5] coverslips, the blocks of agar flipped off, and the impression smear was immediately processed in any one of the methods to be described.

Of the various techniques for the demonstration of mitochondria, one of the most specific and at the same time least complicated is that utilizing the reduction of one of the tetrazols, this reduction being mediated by a DPN-linked

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[5] Mayer's Albumin Fixative, A. H. Thomas Co., Philadelphia, Pennsylvania.

flavoprotein, cytochrome c reductase (4, 5). Kun (6) has shown that a necessary component of the triphenyl tetrazolium chloride-reducing system is present in mitochondria. Triphenyl-tetrazolium chloride (TTC) and neotetrazolium chloride (NTC) were utilized because their formazans are red and dark purple, respectively, colors which, when combined with the blue staining of the DeLamater nuclear stain (7) and the dark red of the Feulgen nucleal reaction, give contrasting colors that make the two structures (nuclei and mitochondria) readily seen and easily differentiated in the same cells. In combining the reduction of TTC or NTC with the specific nuclear stains which require hydrolysis in hydrochloric acid, it is necessary to allow sufficient reduction to occur so that the nuclear processing does not remove all of the formazan. The acid hydrolysis and cold ethanol dehydration both remove some of the formazans, particularly that of TTC.

Method for demonstration of mitochondria with TTC or NTC and nuclear stains:

An agar plate containing 0.1 per cent TTC or NTC in 5 per cent glycerol agar was prepared.

Blocks of cell-bearing agar described above, as yet unfixed, were inverted on the TTC or NTC agar plate, incubated at room temperature for twenty or five minutes, respectively, for *M. thamnopheos* and at 37°C. for two hours or one hour, respectively, for the human tubercle bacilli.

At the end of incubation, the agar blocks were gently turned over, thus leaving some of the cells on the TTC or NTC agar surface and the remainder on the original agar block.

Fixation of the cells in OsO_4 vapor was then carried out and smears were made.

These were immediately placed in 1N HCl at 56°C. and hydrolyzed four to six minutes[6] for *M. thamnopheos* and nine to eleven minutes for the human tubercle bacilli, respectively.

After hydrolysis, they were rinsed for thirty seconds in a rinse solution.[7] The preparations for NTC or TTC controls were placed in the rinse solution, then in distilled water, and finally in the cold ethanol.

The preparations which were also to have the nuclei stained were placed in Schiff's reagent[8] or 0.25 per cent aqueous Azure A[9] to which an equimolecular amount of thionyl chloride had just been added. The cells were stained for two hours.

The coverslips were again rinsed in the rinse solution and in distilled water, and then placed in the cold ethanol.

After eight hours, the smears were removed from the cold ethanol, rinsed once

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[6] Maximum color intensity of the Feulgen reaction may be obtained by small variations of the time and temperature of hydrolysis (8).

[7] 1.0 gm. $K_2S_2O_5$ dissolved in 200 ml. of water, add 1N HCl until pH is 2.3 to 2.4. This rinse removes excess hydrochloric acid from the coverslip and buffers the preparation at the pH which corresponds to that of the Schiff reagent giving maximum color intensity.

[8] Incorporating some of the suggestions of de Tomasi (9) and Tobie (10), the Schiff reagent was carefully prepared as follows. Pour 200 ml. of boiling distilled water over 1.0 gm. of Fuchsin Basic (Dye content 91 per cent, Art. # CF-17, Coleman and Bell Co., Norwood, Ohio) and 1.0 gm. activated charcoal. Stir well. Cool to 50°C. and filter. Cool to room temperature and add 1.0 gm. $K_2S_2O_5$ and stir until dissolved. Add 1N HCl until pH of stain is 2.3 to 2.4. This solution is almost completely colorless and, when stored in a tightly sealed bottle, the pH and clarity of the solution remain stable. This pH was used because it was found to give the most intense coloring.

[9] Azure A Blend, Art. # LAz-9, A. H. Thomas Co., Philadelphia, Pennsylvania.

in room temperature ethanol, counterstained in 0.25 per cent Fast Green FCFS[10] in 95 per cent ethanol for two minutes, rinsed once in ethanol, twice in xylol, and mounted in HSR mounting medium.[11]

The nuclei only may be demonstrated by processing impression smears as described above, using either the Feulgen nucleal reaction (8–10) or the DeLamater stain.

Mitochondria and nuclei may also be demonstrated by adding less than equimolecular amounts of thionyl chloride to the Azure A as used in the DeLamater stain and slightly underhydrolyzing the preparations. Azure A as reduced by thionyl chloride is dark blue but the unreduced dye is a reddish-violet. The former compound stains the nucleus by virtue of its affinity for the aldehyde groups freed during the acid hydrolysis. The latter compound stains a substance removed by acid hydrolysis and localized in the remainder of the cell and particularly in the mitochondria. By balancing underhydrolysis with less than equimolecular amounts of thionyl chloride, double staining of mitochondria and nuclei in the same cells is obtained. Impression smears are processed as described above, using 0.0075 ml. of thionyl chloride added to 10 ml. of 0.25 per cent aqueous Azure A and slightly shorter hydrolysis times. Using the same stain and hydrolysis at 90° C. in 0.3 M trichloracetic acid, which removes all of the nucleic acids, there is no stainable material left in the cell after nine minutes.

Attempts were made to stain the cell wall, using the method of Cassel (11), but they were unsuccessful; however, by a slight alteration some staining was obtained. The cell walls were not as intensely stained as would be considered optimal, but the stain did serve to show the cell walls of most cells. The procedure previously described for the staining of the mitochondria and nuclei in cells that were underhydrolyzed and stained in Azure A containing less than equimolecular amounts of thionyl chloride was modified as follows.

After the preparations were stained in the Azure A and rinsed they were placed in 10 per cent tannic acid for two minutes, rinsed in distilled water, immersed in carbol-fuchsin (diluted 1:8 with water) for approximately two seconds, washed and dehydrated and mounted as previously described without any counterstaining in fast green.

Dilute, aged alkaline methylene blue[12] applied to impression smears for thirty seconds or two minutes, respectively, for *M. thamnopheos* and *M. tuberculosis* var. *hominis* H37Rv also stains two structures. The mitochondrial areas are dark violet; the nuclei are dark blue and the cytoplasm is pale blue.

In cells with mitochondria demonstrated by NTC reduction, the nuclei are stained dark red, and the cytoplasm a lighter red in thirty minutes with carbol-fuchsin (diluted 1:4 with distilled water) as used in the Ziehl-Neelsen acid-fast stain.

OBSERVATIONS

The formazans of triphenyl-tetrazolium chloride and neotetrazolium chloride appeared in the brightly refractile mitochondria, making these structures red or dark violet, respectively. Typical groups of cells with the mitochondria so colored are shown in figures 1, 2, and 11. (Figures 1 through 10, and 17 are of *M. thamnopheos;* figures 11 through 16 and 18 are of *M. tuberculosis* var. *hominis.*) The mitochondria are, in general, polar; however, they are also frequently seen in the center, as in the cell in figure 2. This description of their distribution is not intended as proof that they are mitochondria but merely to emphasize that the granules demonstrated by the specific mitochondrial techniques have a different distribution than the areas that are nuclear.

[10] Fast Green FCF, Dye Content 88 per cent, Art. #NG-9, National Aniline Division, Allied Chemical and Dye Corporation, New York, N. Y.

[11] Harleco Synthetic Resin, Microscopic Mounting Medium, A. H. Thomas Co., Philadelphia, Pennsylvania.

[12] Dilute 1:8 with distilled water; "aged" six months or more.

Neither of the two nuclear stains used stained the mitochondria, that is, the granules which were positive with respect to all of the mitochondrial techniques employed. However, an irregular central area was strongly stained in all of the cells, an area that did not give positive reactions to any of the mitochondrial techniques. Nuclei stained according to the DeLamater technique are shown in the cells in figures 3 and 13.

Feulgen-positive areas are seen in figures 4 and 12. These nuclear areas are frequently paired, and the paired portions are separated by various distances. In long cells there may even be two paired nuclear areas separated by a space (figure 7). This space, as seen in aqueous mounts, often contains a brightly refractile mitochondrion.

Observations on cells in which the mitochondria are shown and on other cells having the nuclei stained indicated that these were two different structures. In aqueous mounts of cells which had the nuclei stained, the brightly refractile mitochondria were clearly seen as separate structures. When the two techniques were applied to the same cells, two different structures were obviously present. The nuclei were stained red with the Feulgen reaction and the mitochondria were stained purple with NTC. Both structures could then be clearly differentiated. Figure 5 shows a cell stained in this fashion. Figures 7 and 14 show cells in which the mitochondria have been stained purple with NTC and the nuclei have been stained blue with the DeLamater stain. Of the combined procedures used, this combination gave the best results from the standpoint of reproducibility, definition, color contrast, and color intensity. Figure 15 shows TTC-stained mitochondria combined with the DeLamater stain.

The procedure of underhydrolysis and staining with Azure A, to which less than equimolecular amounts of thionyl chloride had been added, resulted in reddish-violet mitochondria and dark blue nuclei. If no hydrolysis was used, the nuclei were faded and hardly visible, but the mitochondria or a substance around them were quite dark in color and larger than the mitochondria stained by other methods. These observations apply particularly to *M. thamnopheos*. In the virulent human tubercle bacilli, however, the material which was removed by acid hydrolysis was distributed more uniformly throughout the cytoplasm; there was little staining of the mitochondrial sites by this procedure. Increasing hydrolysis times removed more and more mitochondrial material stained red-violet by the unreduced Azure A, and the blue staining of the nucleus became more and more dense. By balancing underhydrolysis and a small amount of unreduced Azure A, it was possible again clearly to delineate two separate and distinct structures: one, the mitochondrion, red-violet due to staining of a substance removed by acid hydrolysis; the other, the nucleus, dark blue only after acid hydrolysis had freed aldehyde groups of DNA which combined with the reduced Azure A.

Examples of cells so stained are seen in figures 8, 9, and 10. That the materials stained by this method are nucleic acids is suggested by the observation that all stainable material can be removed by hydrolysis in 0.3 M trichloracetic acid at 90°C. for nine minutes. Pollister and Ris (12) state that such hydrolysis removes all the nucleic acids from cytological preparations.

When the cell wall was stained, it appeared as a red line, outlining the cell and surrounding the mitochondria and the nucleus and quite distinct from either. Figure 9 shows the nucleus and mitochondria demonstrated without the cell wall and figure 10 shows the cell wall in a similar preparation.

A similar color combination and staining of the nuclei and mitochondria resulted when dilute, aged alkaline methylene blue was used. Figure 6 shows two cells stained in this fashion with the polar mitochondria and central nuclei clearly differentiated.

Figure 16 shows a cell that had reduced NTC and was then stained with dilute carbol-fuchsin. The polar mitochondria are dark purple; the nuclei, dark red; and the cytoplasm, light red.

Although the figures in the present report clearly show various densities in cells, they do not show the differences in color which make the differentiation of the two structures so striking. The preparations have been photographed in color, however, and have been shown at the 1952 meeting of the National Tuberculosis Association and elsewhere.

Figures 17 and 18 are electron micrographs of virulent human tubercle bacilli (figure 18)[13] and *M. thamnopheos* (figure 17)[14]. The black dense polar granules, whose distribution in the cells is analogous to that of the mitochondria seen in the light or phase-contrast microscopes, are readily visualized. It is not surprising that definite structures corresponding to the nuclei are not seen, since it has repeatedly been demonstrated that nuclear areas may be quite electron transparent in contrast to other portions of the cell (13–16). In cells as electron transparent as the *Mycobacteria*, this contrast would be greatly reduced and, therefore, the nuclei would probably not be readily visualized. In figure 18, however, there is some suggestion of lighter irregular central areas in some cells that may very well correspond to the nuclei. Figure 18 shows that the cell wall is quite different and distinct from the structures that correspond to the mitochondria. Excellent electron micrographs of tubercle bacilli were first published by Lembke and Ruska (17) and subsequently by many others; the electron-scattering granules are uniformly present.

DISCUSSION

The refractile, spheroidal-to-ellipsoidal granules in *Mycobacteria* were admirably described by Robert Koch (18) in his original account of *Mycobacterium tuberculosis* and considered by him to be spores. They have since been described by innumerable investigators, using stained preparations, darkfield, fluorescence (17), and phase microscopy and electron microscopy, and variously interpreted. Since the great majority of these interpretations now have historic interest only, the reader is referred for earlier work to excellent reviews by Knaysi (19) and Wessel (20).

[13] Electron micrograph taken by Dr. James Hillier, R.C.A. Laboratories, Princeton, N. J., in conjunction with another study on the cytology of the tubercle bacilli.

[14] Electron micrograph taken by Mrs. Jean Minkin at the Laboratories of Research and Development, Franklin Institute, Philadelphia, Pennsylvania.

K. A. Bisset (21) refers to the "metachromatic granules" of *Corynebacterium diphtheriae* and to "the granular appearance of *Mycobacterium tuberculosis*" as "the shrunken contents of the enlarged terminal cells," artifacts of drying. Aside from the cogency of innumerable observations of the granules by fully competent investigators, including Koch, Negri, Metschnikoff, and Babes, to mention but a few, the fact that the granules may be seen clearly in living cells and stained intravitally by the tetrazols, Nadi reagent, and Janus green B (2) makes Bisset's contention wholly untenable.

The interpretations of the dense granules in *Mycobacteria* which deserve particular attention are that they are nuclear equivalents, "Nucleoide," "Karyoide" (1), nuclei (22, 23), or mitochondria (24, 2).

The interpretation of Ruska, Bringmann, Neckel, and Schuster (1) rests essentially upon the following observations:

> The young cells of *Mycobacterium avium* stained homogeneously with pyronin, indicating the distribution of ribosenucleic acid throughout the cell. After hydrochloric acid hydrolysis, as expected, the "Nucleoide" only remained basophilic. "There were present, therefore, desoxyribose nucleic acid-containing nuclear equivalents, nucleoids, in a ribose nucleic acid-containing cytoplasm." Cells from older cultures required, for carrying through specific staining, a thorough lipoid extraction. In such cells the pyronin staining appeared at the same sites as the Feulgen nucleal reaction. In such cells "there were present now near the poles of the cells or distributed through the cells nuclear equivalents in the form of karyoids, which contained both ribose and desoxyribose nucleic acids in nucleic acid-free cytoplasm."

The above observations are not questioned. The following additional observations, however, are pertinent, and lead to a different interpretation. The mycobacterial granules are enveloped in definite membranes and are rich in phospholipid (2). Vendrely and Lipardy (25) have shown that ribose- and desoxyribosenucleic acids differ quantitatively, not qualitatively, in their extractability with hydrochloric acid. On hydrochloric acid extraction carefully graduated in time, the ribosenucleic acid is first extracted from the cytoplasm of *Mycobacteria*, then the mitochondrial granules lose their basophilia, and the basophilia of the Feulgen staining nuclei is removed last.

The present writers believe that the basophilic material in some of the granules in the young cells observed by Ruska, Bringmann, Neckel, and Schuster (1) was ribonucleic acid not removed by the hydrochloric acid extraction employed. If the hydrolysis time had been increased, these investigators might have observed a decrease in the number of basophilic granules with only the proximal nuclear ones remaining. Basophilic granules in intentionally under-hydrolyzed mycobacterial cells are shown in figures 8, 9, and 10, labeled *M* (mitochondria). The true Feulgen-positive and DeLamater-positive nuclei (*N*) are distinct from the mitochondrial granules and proximal to them (figures 8, 9, and 10). In the lipoid extracted, hydrochloric-acid–hydrolyzed older cells of Ruska, Bringmann, Neckel, and Schuster (1), the Feulgen staining bodies must have been true nuclei, which would also be expected to be basophilic.

Ruska, Bringmann, Neckel, and Schuster (1) have made an important contribution by showing that the electron-scattering granules in *Mycobacteria* have a high content of metaphosphate, which doubtless is in considerable part responsible for their electron density. As pointed out below, the metaphosphate may also be critically involved in the metachromatic staining of the granules.

Knaysi (19), in his original study of the cytology of *Mycobacterium tuberculosis*, observed the constant presence of the granular bodies and evidence of their division. He also "demonstrated lipid in these bodies, and that was the chief reason why he did not attribute to them a nuclear nature" (22). Later, Knaysi (23) interpreted these granular bodies as nuclei, stressing their division and fusion (26). However, mitochondria also divide and fuse (27–30). Nuclei do contain a low concentration of lipids and this is apparently not entirely phospholipid, whereas mitochondria contain a high concentration; 25 to 30 per cent of the dry weight of mitochondria consists of lipids of which one-half to two-thirds are present in the form of phospholipids (31, 32).

The evidence that the electron-scattering granules of *Mycobacteria* are in fact mitochondria has been set forth in some detail (2, 24). These granules are shown to be loci of oxidative-reductive activities known to be characteristic of enzymes localized in mitochondria; they contain phospholipid and show, in Janus green B, the progression from green to red to colorless characteristic of mitochondria; the granules have smooth contours of minimal areas and are enveloped by definite limiting membranes. Thus, in essential morphologic and cytochemical attributes they resemble the mitochondria of higher animals and plants.

The present work has confirmed and extended the original observations that nuclei and mitochondria may be specifically and differentially stained within the same cells. The nuclei are usually proximal in position to the mitochondria, tend to be more elongate in shape, and are distinguished by giving specific color reactions in the Feulgen and DeLamater nuclear procedures; the mitochondria do not give these specific nuclear color reactions and do give characteristic color reactions to the tetrazols, Nadi reagent, Janus green B, and Baker's and Harman's mitochondrial stains. Further evidence that nuclei and mitochondria are discrete and separate organelles in *Mycobacteria*, *Corynebacteria*, and various coliforms and cocci is presented by Mudd and DeLamater (33).

The present writers believe that nuclei and mitochondria have been stained separately before by Epstein, Ravich-Birger, and Svinkina (34). Illustrations in this paper show large subpolar Giemsa-stained granules; and in other preparations smaller, more proximal, Feulgen-positive granules. It is believed that these were, respectively, mitochondria and nuclei. However, Epstein and his co-workers, unaware of the existence of mitochondria in bacteria, interpreted both structures as nuclei, attributing the obvious differences to differences in staining procedures.

Werner (35) also recognized two types of structure in *Mycobacteria*.

"L'existence dans le cytoplasme des bacilles de *granulations métachromatiques*, plus ou moins nombreuses, opaques, disparaissant avec l'âge, est rapportée. On ne doit pas les confondre avec l'*appareil nucléaire* des bacilles, qui est représenté par des masses rondes ou allongées, généralement centrales, et très transparent aux électrons."

Observations in the present study with dilute Löfflers alkaline methylene blue, a typical basic dye with metachromatic staining ability, were most interesting. When the undiluted dye was used, the entire cell of the tubercle bacilli was stained blue while the polar mitochondrial granules were dark red-violet. Dilution of the dye resulted in a lightly stained cytoplasm, dense blue central nuclear areas, and red-violet mitochondrial granules. A possible interpretation of these various colors and structures is based on the article of Michaelis (36) in which he points out that in solutions of the basic dyes, such as toluidine blue and methylene blue, there may be present three forms of the dye molecule, monomer, dimer, and polymers. Each form is responsible for a characteristically different and specific absorption peak. The α and β forms (the monomer and dimer, respectively) in the case of toluidine blue or methylene blue are indistinguishable to the eye and appear as a blue color, whereas the γ form (the polymer) appears violet. The γ polymer is responsible for metachromatic staining by solutions of these dyes. It is characteristic of nucleic acid to be stained by either the α or β forms without any essential difference between the RNA and DNA. Just as characteristically the γ form does not stain nucleic acids. Polymeric metaphosphate, however, does stain metachromatically (36). Alternatively, the red-violet of the mitochondrial granules may have been due to methylene violet present in the aged methylene blue (2).

The reduction of triphenyl-tetrazolium chloride has been developed as a test of total viability for suspensions of tubercle bacilli (37).

SUMMARY

In *Mycobacterium thamnopheos* and *Mycobacterium tuberculosis* var. *hominis* H37Rv, two different structures have been observed. The first, usually polar, is a spheroidal to ellipsoidal structure which does not stain with the typically nuclear stains but is analogous in its reactions to mitochondria as found in other cells. The second structure is stained by the nuclear stains and does not give any of the mitochondrial reactions. As the evidence is clear, from a biochemical and genetic standpoint, that bacteria are cells as other cells, it seems both fitting and necessary on the cytological evidence presented to call the first structures mitochondria and the second, nuclei.

SUMARIO

La Citología del Bacilo Tuberculoso con Referencia a Mitocondrias y Núcleos

En el *Mycobacterium thamnopheos* y el *Mycobacterium tuberculosis* var. *hominis* H37Rv, se han observado dos distintas estructuras. La primera, habitualmente polar, varía de esferoidea a elipsoidea y no toma los colorantes típicamente nucleares, pero es análoga en sus reacciones a las mitocondrias observadas en otras células. La segunda toma los colorantes nucleares y no acusa ninguna de las reacciones de las mitocondrias. Como hay pruebas indudables, desde los puntos de vista bioquímico y genético, de que las bacterias son células como otras, parece apropiado a la par que necesario, a la luz de los datos citológicos presentados, llamar a la primera estructura mitocondria y a la segunda núcleos.

RESUME

La cytologie du bacille tuberculeux en relation avec les mitochondries et les noyaux

Deux différentes structures ont été observées dans le *Mycobacterium thamnopheos* et le *Mycobacterium tuberculosis var. hominis* H37Rv. La première, habituellement polaire, est une structure sphéroïdale ou ellipsoïdale qui ne prend pas la coloration avec les colorants nucléaires spécifiques, mais dont les réactions sont analogues á celles présentées par les mitochondries dans les autres cellules. La deuxième structure est colorée par les colorants nucléaires et ne donne aucune des réactions mitochondriales. Comme du point de vue génétique et biochimique, on possède la preuve que les bactéries sont des cellules comme les autres, il semble à la fois acceptable et nécessaire, d'après les données cytologiques présentées, de dénommer la première structure mitochondrie et la deuxième noyau.

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EXPLANATION OF PLATES

PLATE I

Mycobacterium thamnopheos, Magnification 3,880×

Mitochondrion = *M* Nucleus = *N*

Fig. 1: Cells from a twenty-four-hour culture showing the mitochondria as demonstrated by neotetrazolium reduction.

Fig. 2: Cells from a six-hour culture hydrolyzed fourteen minutes at 57°C. in 1N HCl following OsO_4 fixation. The formazan of neotetrazolium persists in its mitochondrial location even after hydrolysis.

Fig. 3: Cells from a twenty-four-hour culture showing the nuclei as demonstrated by the DeLamater nuclear stain. Hydrolysis was carried out for seven minutes at 57°C. in 1N HCl. Fast Green was used as a counterstain.

Fig. 4: Cells from a twenty-four-hour culture showing the nuclei as demonstrated by the Feulgen reaction.

Fig. 5: A cell from an eighteen-hour culture in which the mitochondria are demonstrated by neotetrazolium and the paired nuclear areas by the Feulgen reaction.

Fig. 6: Two cells from a six-hour culture that have been stained with dilute alkaline methylene blue. The nuclei are dark blue, the mitochondria red-violet, and the cytoplasm is light blue.

Fig. 7: Cells from a twenty-four-hour culture in which the nuclei, single and paired, are stained dark blue by the DeLamater nuclear stain and the mitochondria are demonstrated by the violet of neotetrazolium reduction.

Fig. 8: Cells from an eighteen-hour culture that were slightly underhydrolyzed (four minutes in 1N HCl at 57°C.) prior to staining in Azure A, to which less than equimolecular amount of thionyl chloride had been added.

Fig. 9: A cell from a twelve-hour culture that has been stained in the same manner as the cells in figure 8.

Fig. 10: A cell from the same culture as that of figure 9 and treated with the same staining procedure except that the cell wall has also been stained and shows as a fine penciled line around the entire cell.

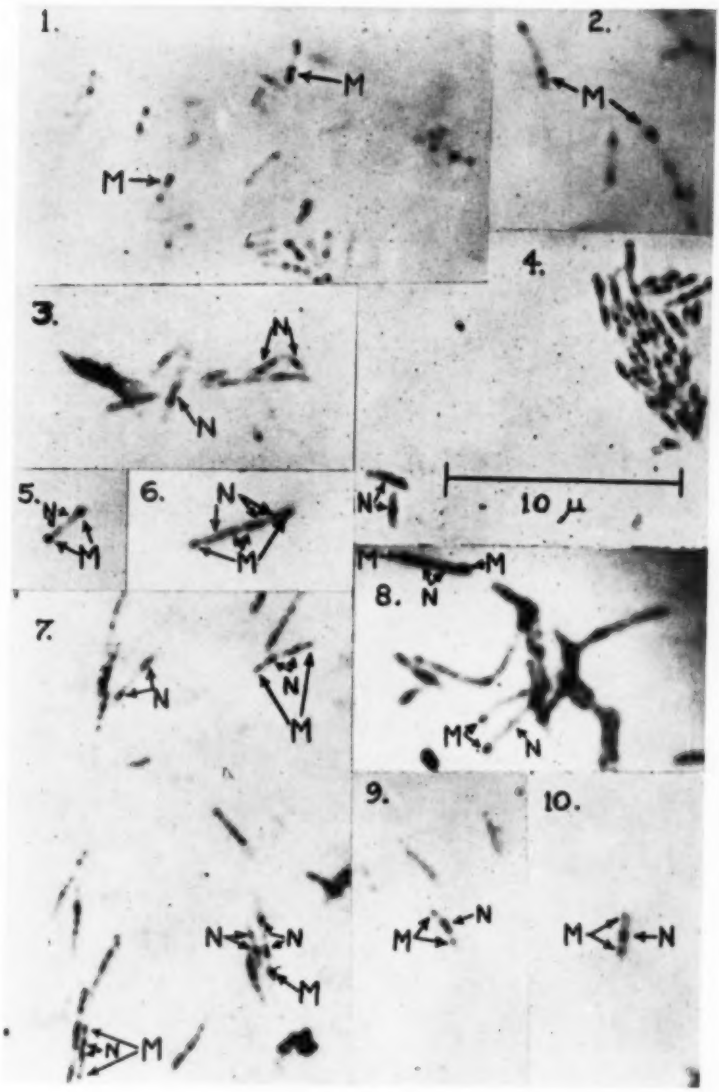

PLATE I

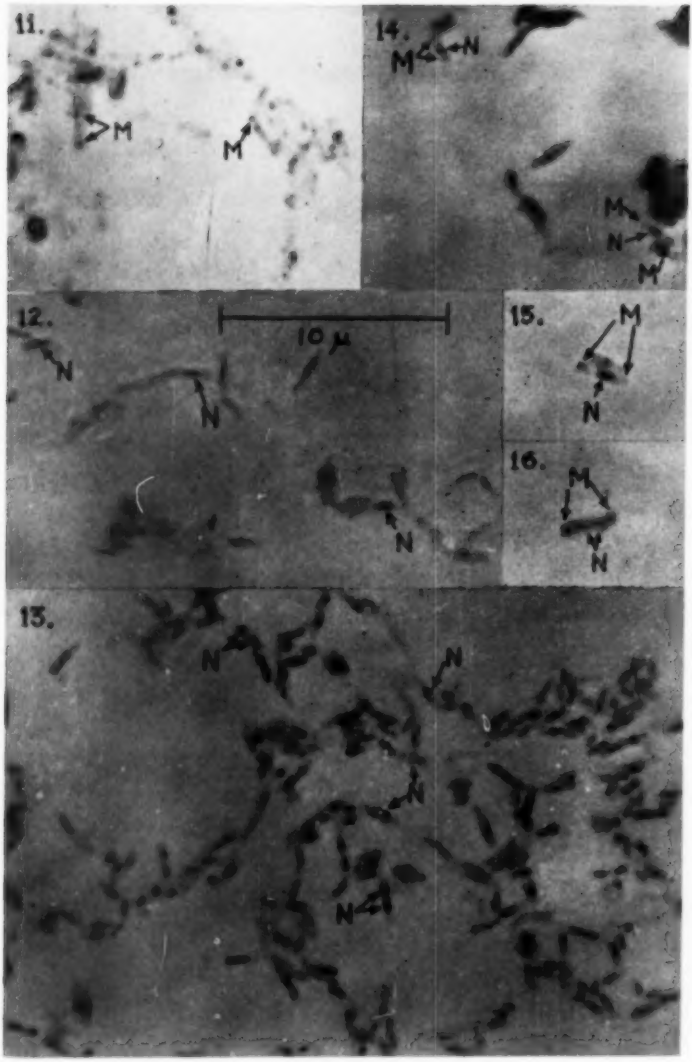

PLATE II

Mycobacterium tuberculosis var. *hominis* H37Rv

Mitochondrion = *M* Nucleus = *N*

Fig. 11: Cell from a four-day culture in which the mitochondria are demonstrated by neotetrazolium reduction.

Fig. 12: Nuclei in cells of a four-day culture as shown by the Feulgen reaction.

Fig. 13: Cells from the same culture as figure 12 with the nuclei demonstrated by the DeLamater nuclear stain.

Fig. 14: Mitochondria and nuclei in the same cells as shown by neotetrazolium reduction and the DeLamater nuclear stain, respectively.

Fig. 15: In this cell the nucleus is demonstrated by the DeLamater stain and the mitochondria by the reduction of triphenyl tetrazolium.

Fig. 16: A cell from a culture grown for two weeks, using an inoculum from a routine tuberculous sputum. The mitochondria are shown by neotetrazolium reduction and the nuclei by greater affinity for the basic dye in the carbol fuchsin as used in the Ziehl Neelsen stain.

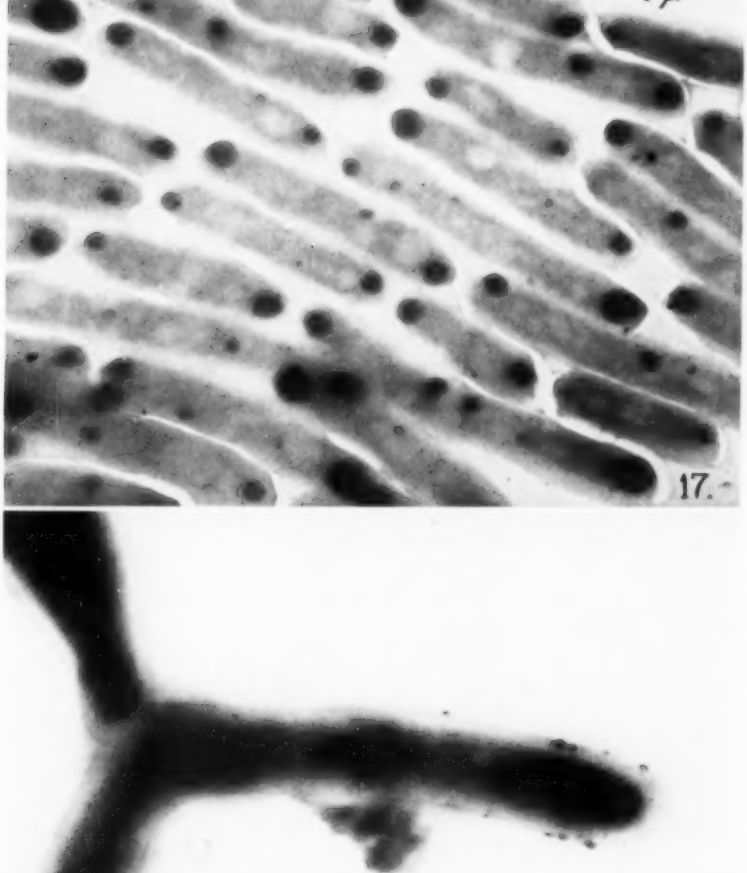

PLATE III

Fig. 17. An electron micrograph of *M. thamnopheos* fixed for one minute in OsO_4 vapor, showing the polar position of the dense spheroidal bodies which are believed to be the granules seen in the light microscope and which, in all the properties examined, correspond to mitochondria. Note that in some longer cells there are also dense granules centrally located which correspond to loci in which mitochondria are frequently seen in the light microscope. The cytoplasm is very electron transparent and this may explain why the nuclear areas are not visualized.

Fig. 18. An electron micrograph of *M. tuberculosis* var. *hominis* H37Rv, fixed for one minute in OsO_4 vapor, which shows the dense polar granules, the alternating light and dark areas that represent nuclei and cytoplasm, respectively, in cells of other genera, and the clearly defined cell wall.

TUBERCULOSIS CONTROL IN HOSPITAL PERSONNEL[1, 2]

A Review

H. McLEOD RIGGINS

(Received for publication May 26, 1952)

Recent developments in the treatment of tuberculosis, especially in chemotherapy and excisional surgery, have focused attention anew upon the place of the general hospital in the treatment of this disease. The public has become increasingly aware of these new trends, and expects the community hospital, to which it contributes, to provide facilities for its care. Health and sickness insurance companies, including the Associated Hospital Service (Blue Cross Plan), have recognized this trend and are partly meeting the demands of their policyholders by allowing benefits for tuberculosis patients admitted to general hospitals for the purpose of pneumothorax, pneumoperitoneum, and thoracic surgery. These developments have resulted in the treatment of increasing numbers of tuberculous patients in general hospitals; consequently, there has been renewed interest in the problem of tuberculosis in hospital personnel.

It should not be inferred from the title of this review that the control of tuberculosis in certain hospital personnel is a special problem differing from the control of the disease in the general population. Although there are certain specific differences, tuberculosis control in hospitals and in the community at large is basically and fundamentally the same. Such factors as adequate diet, sanitary living and working conditions, health education, adequate case finding and definitive diagnosis, effective treatment, and prompt rehabilitation apply equally to tuberculosis control in hospital personnel and in the community at large.

One problem peculiar to tuberculosis control in hospitals is the possibility of compensation of exposed personnel who develop the disease. This has not only become an important problem in the control of tuberculosis in hospitals but has affected singificantly the attitude of hospital administrators with regard to the admission of tuberculous patients to general hospitals.

Instead of overemphasizing the dangers of exposure to infectious cases of tuberculosis within the hospital, it should be stressed that approximately 98 per cent of personnel having had proved hospital exposure do not develop the disease. It is more important to determine and emphasize ways and means of protecting those who come in contact with known or unknown cases of active disease than to overemphasize the undue hazards which can be minimized greatly by the use of simple and effective precautions.

It is reliably estimated (1) that not more than 10 per cent of all general hospitals allocate beds for known tuberculous patients. Despite this general policy,

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[2] Presented before the Nursing Session, as part of the symposium *Is Nursing in Step with Research?*, at the 48th annual meeting of the National Tuberculosis Association, Boston, Massachusetts, on May 26, 1952.

it is well known that thousands of unknown cases of the disease are admitted to general hospitals for treatment of other conditions.

The following documented facts emphasize why tuberculosis in certain hospital personnel is still an unsolved problem:

Necropsy studies by Medlar (2) at Bellevue Hospital on persons who died from nontuberculous causes revealed tuberculous cavities in 5 per cent of 1,225 autopsies.

Roentgenographic surveys of admissions to general hospitals have disclosed active or possibly active tuberculosis in 0.6 to 1.1 per cent of patients not previously known to have the disease (1). Applying the smaller figure to adults admitted to general hospitals, it has been estimated that approximately 40,000 *unknown* cases of tuberculosis are admitted to general hospitals every year. This figure gives some idea of the frequency of exposure of ward personnel to unknown cases of the disease.

Tuberculin conversion rates in hospital personnel: During the past two decades, numerous tuberculin-testing studies in different population groups, including high schools, colleges, and medical and nursing students, have shown three striking findings (3–5):

a. There is a wide geographic range in the percentage of positive tuberculin reactors among young adults in different sections of the country.

b. There has been a constant decrease in the proportion of positive tuberculin reactors during recent years, indicating a decline of tuberculous infection in young adults in general throughout the country.

c. Hospital personnel who have negative tuberculin tests and who are frequently exposed to infectious tuberculosis within hospitals become positive reactors much more rapidly than do other hospital personnel or young adults not working in a hospital environment (6–11). In Connolly's recent survey and summary of the literature on this subject (12), she noted, from studies on student nurses in general hospitals, that the proportion of tuberculin reactors on graduation ranged from 53.4 per cent in three Minneapolis general hospitals to 100 per cent in the Philadelphia General Hospital. In 1936, Amberson and Riggins (6) and, again in 1940, Riggins and Amberson (7) emphasized that primary tuberculous infection among student nurses at Bellevue and Lenox Hill Hospitals was more rapid than that in somewhat similar young adult groups working outside of hospitals. In the studies in these two hospitals between 1930 and 1940, approximately 90 per cent of the Bellevue student nurses and 92 per cent of the Lenox Hill student nurses who had a negative Mantoux originally became positive reactors during their three-year training course.

Essentially similar tuberculin conversion rates have been found among student nurses by other investigators in the East, while considerably lower conversion rates have usually been found among student nurses in Midwestern training schools. As already indicated, tuberculin conversion rates in young adults, including hospital personnel, vary significantly in different parts of the country. The less rapid tuberculin conversion rate among student nurses in the Midwest than among those in the East is probably an expression of the fact that there is considerably less tuberculosis in certain Midwestern than in many Eastern

cities. It is therefore logical to assume that the differences in the tuberculin conversion rates are not primarily due to differences in hospital aseptic techniques but are significantly related to the prevalence of tuberculosis within the community.

The point most pertinent to this discussion, however, is that the conversion rates among student nurses in both the Midwest and East are more rapid and higher than the rates for college students and other young adult groups in the same areas. These findings strongly indicate that, in so far as primary tuberculous infection is concerned, being a student nurse is considerably more hazardous in large Eastern hospitals, and somewhat more hazardous in large Midwestern hospitals, than being a secretary in a bank. The question naturally arises: Should primary tuberculous infection as evidenced by conversion of the tuberculin test be used as a measure of the degree or extent of the tuberculosis hazard in a specific environment? From the writer's experience and that of others, this question must be answered in the affirmative.

An even more difficult question is whether or not primary tuberculous infection occurs more rapidly in student nurses and other personnel who have part of their training on tuberculosis services or in tuberculosis sanatoriums than among student nurses and other personnel not so exposed. The pros and cons of this controversy will be presented briefly.

Hastings and Behn (13) believe that the chances of tuberculous infection for student nurses working on tuberculosis services or in sanatoriums are greater than for those not working on such services. Their tuberculin conversion rates for students who had experience on tuberculosis services was 50.8 per cent compared with 39.2 per cent for nurses who did not work on tuberculosis services. These conversion rates are for the entire three years of training and the difference does not seem too convincing. However, Schwartz (14) found somewhat more convincing conversion rates among student nurses affiliated with Trudeau Sanatorium. Of a total of 234 student nurses studied, he found 25 per cent of the nonreactors converted after only two months' affiliation at Trudeau. In 1947, Myers and associates (15) reported that after the discontinuance of the tuberculosis service at Fairview Hospital there was a marked reduction in the tuberculin conversion rate among student nurses at that hospital, i.e., from 100 per cent conversion in 1932 to 50 per cent conversion in 1939, and only 16 per cent conversion in 1946. They believe that this marked reduction in the conversion rate was due, not only to the discontinuance of the tuberculosis service, but also to the use of a strict contagious-disease technique and to the guarding of hospital personnel from unknown tuberculosis admissions.

Barnwell and Beckerman (16) found that the tuberculin conversion of nonreactors was no more rapid following exposure on the tuberculosis service than that following experience on other services. Muschenheim, Bunn, and Lansdown (17) also reported that they found no greater conversion rates among student nurses who worked on the tuberculosis service than among those who had worked on the pediatric service. Similar experiences have also been reported by Pollak and Cohen (18), Shoor (19), and Brahdy (20). Although Riggins and Amberson

(7) reported that the tuberculin conversion rates for student nurses at Bellevue were more rapid than in non-hospital personnel, nevertheless, they too were of the opinion that the tuberculin conversion rate was no greater following exposure on the chest service than following exposure on the general medical wards.

The pertinent fact, however, is that tuberculin conversions were more rapid in student nurses at Bellevue and at other hospitals than in college students and other young adults. These findings strongly indicate that tuberculous infection among student nurses and certain other hospital personnel is, not only an unsolved problem, but a greater one for these hospital personnel than for young adults not exposed at their place of work.

Second only to students of nursing, medical students have been studied from the point of view of tuberculous infection and morbidity. In general, it appears that the annual tuberculin conversion rates for medical students are somewhat less than those for student nurses. The annual tuberculin conversion rates (previously referred to) at Harvard Medical School were 12 to 13 per cent; at Louisiana State, 5 to 6 per cent; and at Northwestern, 7 to 8 per cent. The tuberculin conversion rate at the Women's Medical College of Pennsylvania was considerably higher. In a report from that school, Morris (21) states that by the time of graduation all medical students had become positive reactors. Tuberculin conversion rates in Eastern medical students are in considerable contrast with those in the Midwest, just as are conversion rates among student nurses. Studies by Myers and associates (22) in 1943 showed the annual tuberculin conversion rate for medical students to be approximately 4 per cent per year. In another study, however, Myers and co-workers (11) reported that, of a total of 65 interns, approximately 75 per cent developed a positive reaction during their internship.

Studies on the tuberculin conversion rates of non-hospital young adult groups, particularly those of West, Schaeler, and Myers (23) and Plunkett and Katz (5), show the tuberculin conversion rates in these groups to be considerably less than those reported for nurses and medical students. Plunkett and Katz estimated the rate of infection among normal-school students in upper New York State to be 3.7 per cent per year. The Minneapolis group found the conversion rate for non-hospital personnel as low as 1.0 per cent per year.

From these and other sample studies, it may justifiably be concluded that the great preponderance of evidence indicates that the opportunity for tuberculous infection is considerably greater for nurses, medical students, and certain other exposed hospital personnel than it is for college and normal-school students and other young adults not working in hospitals.

Tuberculosis morbidity in hospital personnel: Although the available data indicate that primary tuberculous infection occurs more rapidly and in a higher percentage of certain hospital personnel than in somewhat comparable groups of the general population (normal-school and college students), the important question remains: Are certain groups of hospital personnel, notably student nurses, interns, and laboratory workers, more prone to develop clinical tuberculosis than other groups of young adults within and outside of the hospital but not similarly exposed? Despite the fact that numerous studies have been

made concerning tuberculosis morbidity among hospital personnel during the past two decades, very few comparable studies have been made on similar groups outside of the hospital environment. Moreover, most studies fail to give the annual morbidity rates but, instead, give the incidence of tuberculosis over a given period of years. It is difficult to compare different studies, even those dealing only with hospital personnel, and it is more difficult to compare morbidity rates of hospital personnel with those of young adults outside of the hospital environment. A comparison of morbidity rates, just as a comparison of infection rates, must also take geography into account since these rates differ significantly in different geographic areas.

Tuberculosis morbidity rates among student nurses: Tuberculosis morbidity rates among student nurses vary significantly in different parts of the country. As a rule, if the tuberculosis mortality rates for the community are relatively low, the tuberculosis morbidity rates for hospital personnel are relatively low; but, if the tuberculosis mortality rates for the community are relatively high, the morbidity rates for student nurses are high. It is obvious, therefore, that high tuberculosis morbidity rates in hospital personnel are relative and are not related solely to working in a hospital but are significantly related to the amount of tuberculosis in a given community or geographic area. Morbidity rates for student nurses in Eastern schools vary from a low of 0.2 per cent per year to a high of 4.8 per cent per year. The average annual morbidity rates range from approximately 0.5 per cent to 1.5 per cent per year.

The comparison of morbidity rates for student nurses with those of medical students is difficult. Nevertheless, the rates for the nurses appear appreciably higher. This is not surprising since females appear to be somewhat more susceptible than males in these two age groups. The available data, though limited, also suggest that the tuberculosis morbidity rates among student nurses are considerably higher than among other hospital personnel, with the possible exception of laboratory workers. The evidence also shows that tuberculosis morbidity for student nurses and laboratory workers appears to be greater than for young adult groups not working in a hospital environment.

Tuberculosis morbidity rates among medical students: Tuberculosis morbidity rates for medical students vary significantly in the different medical schools and are generally higher for Eastern schools than for Western and Midwestern schools. Even in the Eastern schools, the rate varies between 0.35 per cent and 4.1 per cent. These rates are for the full four years of medicine. The highest rate was found by Morris (21) for female medical students at the Women's Medical College of Pennsylvania in studies made between 1932 and 1944. The highest morbidity rate reported for medical students in Midwestern schools (11) was 3.9 per cent for the full four-year course. At approximately the same time, the rate for law students at the same university was less than one-half of 1 per cent; and at the College of Education, approximately 0.2 per cent. These figures strongly suggest that tuberculosis morbidity among medical students in Midwestern schools is considerably higher than that for the average adult population outside of the hospital and laboratory environment.

The Prophit (24) survey in England showed that approximately 2 per cent of male medical students and 4 per cent of female students developed tuberculosis during their four-year course. This compares with an incidence of 0.2 per cent in male "controls" within the same area.

In summary, it may be concluded that in so far as valid data allow inferences, tuberculosis morbidity rates are considerably higher for student nurses, laboratory workers, and medical students than for other hospital personnel not having similar exposure; moreover, they are considerably higher than for young adults not working in a hospital environment.

Tuberculosis mortality in hospital personnel: Although studies of tuberculosis among hospital personnel (student nurses and medical students, principally) show high primary tuberculous infection and high morbidity rates, the mortality rates are extremely low, almost without exception. The great majority of tuberculosis deaths which have been reported in hospital personnel studies occurred prior to the practice of frequent roentgenographic examinations and resulted from disease which was usually well advanced when discovered. These very low mortality rates emphasize the tremendous value of *early* diagnosis and *adequate* treatment, and suggest effective ways to improve the control of tuberculosis in hospital personnel. While it is of the greatest importance to prevent death from tuberculosis in hospital personnel, the achievement of that goal represents only partial success. It is also of great importance to further minimize tuberculous infection and morbidity as well as to prevent tuberculosis mortality. Effective therapy should not permit or encourage ineffective prevention.

Evaluation of Tuberculosis Hazards for Hospital Personnel

In attempting to evaluate the relative tuberculosis risks for hospital personnel versus that of non-hospital personnel, a number of important factors must be considered. One such factor is the frequency of roentgenographic examination of the chest. If such examinations are made every three to four months, more tuberculosis will be discovered than if they are made only when symptoms indicate the need for them. Usually the reports on the morbidity rates for hospital personnel are based on roentgenographic examinations at frequent and periodic intervals; whereas, the morbidity reports for non-hospital personnel are usually based on films taken at infrequent intervals. It is well known that primary and postprimary tuberculous infection may develop asymptomatically and its clinical and roentgenographic evidence may disappear equally rapidly. If roentgenographic examinations are made infrequently, therefore, many such lesions will not be discovered. The importance of this one factor in determining morbidity rates is emphasized by the Harvard Medical School investigators (8) who reported that, when roentgenograms were taken only when symptoms indicated their need, the annual incidence of tuberculosis was 0.9 per cent; but when films were obtained at frequent regular intervals, the annual incidence immediately rose to 2.2 per cent, or more than twice as great. These investigators concluded that the apparent increase in the morbidity rates was largely due to the more frequent roentgenographic examinations and was more apparent than real.

Suggestions for the Better Control of Tuberculosis in Hospital Personnel

As in other groups of persons, many important factors are involved in the prevention or the development of tuberculosis in hospital personnel. Some of the more important of these factors are native resistance, acquired partial immunity, age, sex, race, nutritional state, type of working and living conditions, adequate rest, recreation facilities, and the degree and severity of exposure to tubercle bacilli. Specific and practical measures which hospital administrators can take to minimize tuberculous infection, morbidity, and mortality are already in routine practice in many hospitals but are not adequately used in numerous others; and little or no precautionary measures are taken in still other hospitals.

Measures to control tuberculosis effectively in hospital personnel are not only concerned with personnel but also with patients admitted to the hospital, some of whom have unknown tuberculosis.

In order to prevent unnecessary exposure of hospital personnel to patients having *unknown* tuberculosis who are admitted to hospitals for the treatment of some other condition, *all* persons admitted to hospitals should have chest roentgenograms. In 1948, of 4,539 hospitals surveyed, only 247, or a little more than 5 per cent, reported that chest roentgenograms were made on all admissions (1). These and other data previously cited indicate the dangers to certain hospital personnel of exposure to *unknown* cases of active tuberculosis.

This danger can be greatly minimized by obtaining a chest roentgenogram when the patient is first admitted; in mental institutions, where patients remain for long periods of time, the roentgenographic examination should be repeated periodically.

All patients with possible tuberculous lesions should have a three-day concentrated sputum specimen examined for tubercle bacilli and, if negative, the gastric washings should be cultured. If feasible, culture of the sputum for tubercle bacilli should also be made.

Patients with active or possibly active tuberculosis should be isolated. Such a policy might necessitate the creation of a small chest or tuberculosis ward in large hospitals, particularly if they are city, county, or state hospitals. If the hospital is relatively small, a few beds would probably be sufficient to accommodate the tuberculosis suspects or active cases until the condition for which they were originally admitted to the hospital could be cared for adequately. These possible dangers emphasize the great need for small chest units in all general hospitals.

Health Program for Hospital Personnel

The establishment of a well-rounded health program designed to protect and improve the general health of all employees is essential for the control of tuberculosis in hospital personnel.

Education of Patients and Hospital Personnel

Efforts should be made to educate patients how not to spread bacilli in their immediate surroundings. It is essential to educate student nurses and other exposed hospital personnel early in their training concerning the necessary precautions which they should take to protect themselves against the unknown as well as the known tuberculous patient. Since there are large numbers of unknown tuberculous patients in general medical

and other wards, it is necessary that ward personnel observe simple but effective precautions, particularly if admission roentgenograms are not obtained. The exposed personnel should be informed that their work entails certain possible risks which can be significantly minimized, however, provided proper precautions and good living and working habits are observed.

Simple precautionary measures such as the following have been found to be effective:

a. Gowns should be worn in contaminated areas.
b. Both patient and personnel should wear the proper type of face mask when the employee is working in contaminated areas and in close proximity to infectious patients.
c. Rubber gloves should be used when handling certain contaminated materials such as sputum cups and containers.
d. Proper care should be exercised in the disposal of sputum and other infectious materials.
e. Frequent and adequate washing of the hands is helpful.

Cleanliness and other measures which may reduce or kill tubercle bacilli in contaminated areas should be practiced.

Well-planned, practical studies should be made to clarify many controversial and precautionary proposals such as the use of ultraviolet light in wards and other contaminated areas.

Hospital personnel should be taught to carry out all necessary precautions in such a manner as to least offend the patient. If such practical procedures as are suggested are constantly observed and if an adequate health program is actively practiced, it is doubtful if the more strict contagious-disease techniques are necessary.

Pre-employment roentgenograms: All hospital personnel should have pre-employment chest roentgenograms. If pulmonary pathology is detected, final disposition of the applicant should depend upon the exact diagnosis following thorough study.

Tuberculin testing: All hospital personnel who may come in contact with known or unknown tuberculosis within the hospital should have tuberculin tests, preferably by the Mantoux method. If the first test is negative, the test should be repeated with the second-strength dose of tuberculin. Personnel should be retested with tuberculin every three to four months so long as they remain negative.

Subsequent roentgenographic examinations: The frequency of subsequent roentgenographic examinations depends upon a number of factors, some of the more important of which are age of the employee, frequency and degree of exposure to infection within the hospital, status of the pre-employment and subsequent tuberculin test, and other circumstances which might predispose to the development of tuberculosis. Chest roentgenograms are not essential as long as the tuberculin test remains negative. Following conversion of a negative tuberculin in such exposed groups as student nurses, laboratory workers, and other young adults (less than thirty years of age) who are, or may be, exposed to tuberculosis in their daily work, roentgenographic examination should be made every four to six weeks for six months immediately after conversion, every two months for an additional six-month period, and every three months thereafter. This extra precaution appears necessary since many investigators, including the writer, have found that, if recent tuberculin converters are to develop roentgenographic or clinical evidence of disease, this usually occurs within six to twelve months after the person becomes a reactor. Frequently exposed young adults (less than thirty years of age) with a positive pre-employment tuberculin test should have a routine roentgenographic examination every three months. For adults more than thirty years of age, examination every

four to six months is usually adequate. For personnel who are infrequently exposed to known or unknown tuberculosis within the hospital, chest roentgenograms may be obtained less frequently, depending upon individual circumstances. In general, an annual examination is probably adequate.

BCG vaccination: Although it should be re-emphasized that BCG vaccination plays only a minor role in the prevention of clinical tuberculosis, nevertheless, the suggestions made by the American Trudeau Society (25) in 1949 are recommended. All frequently exposed and possibly vulnerable young adults who have a negative tuberculin test should receive BCG vaccination and should be revaccinated periodically as individual circumstances warrant.

SUMMARY

An analysis of the available and valid data justifies the conclusion that primary tuberculosis infection rates, as indicated by the conversion of the tuberculin test, are frequently quite high for students of nursing and medicine and certain other exposed hospital personnel, especially laboratory workers. These rates are much higher than those for young adults working in a nonexposed hospital environment or for young adults working outside of hospitals.

Although the available data do not give such a clear-cut answer concerning morbidity, there appears to be little doubt that tuberculosis morbidity among nurses, medical students, certain interns, and other exposed young adults is frequently higher than for nonexposed personnel within the hospital or for young adults having other occupations.

Tuberculosis mortality rates among even the more exposed and vulnerable hospital personnel groups are extremely low despite the high infection and morbidity rates. This is probably due largely to earlier diagnosis and more adequate treatment than in the case of non-hospital personnel.

An adequate general health program for all hospital personnel, which includes pre-employment, subsequent, and periodic tuberculin testing and chest roentgenographic examinations (as previously outlined), simple but effective precautionary measures as already indicated here and described in detail in *Safer Ways in Nursing* (26), BCG vaccination for certain vulnerable and exposed personnel, and chest roentgenograms for all hospital admissions greatly reduces the tuberculosis risk.

The experience of the writer and others indicates that it is possible to reduce the risk of tuberculosis to a degree that is little, if any, greater for hospital personnel than for young adults of the general population.

SUMARIO

LA LUCHA ANTITUBERCULOSA EN EL PERSONAL HOSPITALARIO

El análisis de los datos fidedignos disponibles justifica la conclusión de que las tasas de infección tuberculosa primaria, según indica el viraje de la prueba de la tuberculina, son frecuentemente bastante altas para los estudiantes de medicina y de enfermería y cierto otro personal hospitalario expuesto al mal, y en particular técnicos de laboratorio. Esas tasas son mucho más altas que las arrojadas por los jóvenes que trabajan en un ambiente hospitalario indemne o fuera de los hospitales.

Aunque los datos disponibles no facilitan una respuesta tan concreta en cuanto a morbi-

dad, cabe poca duda de que la morbidad tuberculosa entre enfermeras, estudiantes de medicina, ciertos internos y otros adultos jóvenes expuestos a la dolencia es frecuentemente más alta que para el personal hospitalario no expuesto o que para los jóvenes dedicados a otras ocupaciones.

Los coeficientes de mortalidad tuberculosa, aun entre los grupos más expuestos y vulnerables del personal hospitalario, son sumamente bajos, a pesar de las elevadas tasas de infección y de moribidad. Esto se debe probablemente en gran parte al diagnóstico más temprano y al tratamiento más adecuado en ellos que en el personal no hospitalario.

El riesgo que corre, con respecto a tuberculosis, el personal hospitalario experimenta una gran reducción cuando se instituye un adecuado plan general de salud para todo el personal hospitalario, comprendiendo: comprobación con tuberculina y radiografías torácicas antes y después del empleo y periódicamente en la forma bosquejada, precauciones sencillas pero efectivas según se indica aquí y se pormenoriza en Asistencia Más Inocua del Enfermo, vacunación BCG para cierto personal vulnerable y expuesto y radiografías torácicas para todos los recibidos en el hospital. Las observaciones del A. y de otros indican que es posible reducir el riesgo que entraña la tuberculosis a tal punto que sea poco mayor, si lo es, para el personal hospitalario que para los jóvenes de la población general.

RESUME

Contrôle de la tuberculose dans le personnel hospitalier

Une analyse des données valables disponibles justifie la conclusion que les taux de primo-infection tuberculeuse, tels qu'ils dérivent du virage du tuberculin-test, sont souvent très élevés chez les élèves infirmières et les étudiants en médecine ou autres membres du personnel hospitalier exposés à la contamination, et tout particulièrement chez les techniciens de laboratoire. Ces taux sont très supérieurs à ceux obtenus chez les jeunes gens travaillant dans un milieu hospitalier non exposé à l'infection ou chez ceux qui travaillent hors des hôpitaux.

Bien que les données dont on dispose ne donnent pas de réponse précise à l'égard de la morbité, il semble peu douteux que la morbidité tuberculeuse parmi les infirmières, les étudiants en médecine, certains internes et autres jeunes gens exposés à la contagion soit souvent supérieure à celle observée parmi le personnel non exposé, ou chez les jeunes gens se livrant à d'autres occupations.

Les taux de mortalité par tuberculose parmi les groupes de personnel hospitalier les plus exposés et les plus vulnérables sont extrêmement bas, en dépit de taux d'infection et de morbidité élevés. Ceci est sans doute, en grande partie, la conséquence d'un diagnostic plus précoce et d'un traitement plus adéquat que dans le cas d'un groupe de personnel non hospitalier.

Un programme adéquat d'hygiène générale pour l'ensemble du personnel hospitalier comprenant des tests à la tuberculine avant l'emploi et ensuite des tests périodiques, des radiogrammes du poumon comme il a été décrit précédemment, des mesures prophylactiques simples mais efficaces, telles qu'elles sont esquissées ici et décrites en détail dans "Safer Ways in Nursing", des vaccinations par le BCG pour une certaine catégorie de personnel vulnérable et exposé, ainsi que des radiogrammes du poumon pour tout malade admis à l'hôpital, réduit considérablement le risque de contamination tuberculeuse du personnel hospitalier. L'expérience acquise par ces auteurs et d'autres investigateurs indique qu'il est possible de réduire le risque d'infection tuberculeuse à un degré, qui n'est qu'à peine ou pas plus élevé pour le personnel hospitalier, que pour les jeunes gens de la population générale.

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TUBERCULOSIS AMONG JEWS[1]

Mortality and Morbidity Among Different Jewish Ethnic Groups. Tuberculosis Among Yemenite Jews. Etiologic Factors.

JOSEPH RAKOWER

(Received for publication April 21, 1952)

Introduction: The mass immigration into Israel during the past four years provides material of special interest for the tuberculosis epidemiologist. At times entire Jewish populations have been transferred from the Diaspora to Israel from Iraq, Yemen, and Bulgaria, and have been united with different stocks of the same original extraction who have lived for the past two thousand years under entirely different conditions. Although the immigration continues, there is a mass of gathered material which has already thrown new light upon certain old epidemiologic problems.

There are now four ethnic groups in Israel:

Ashkenazi comprise 50 per cent of the population and originate principally from Eastern and Central Europe.

Sephardi comprise 30 per cent of the population and originate from the Mediterranean countries of North Africa, Syria, Lebanon, and Turkey.

Oriental communities comprise 15 per cent of the population and originate from Iraq, Persia, Kurdistan, Afghanistan, and Bukhara.

Yemenite Jews comprise 5 per cent of the population and originate from the southern part of the Arab Peninsula.

Two thousand years of life in the Diaspora have had a great influence on the anthropologic characteristics of the above-mentioned groups. The Ashkenazi Jews are of middle height, 85 per cent mesocephales, are 25 per cent blond, and have predominantly blood group A (19). The Sephardic group are 68 per cent mesocephales, 30 per cent brachycephales, are 5 per cent blond, and have most frequently blood group B. The Oriental Jews resemble the Sephardi with the exception of the B'nai Israel (East Indian Jews) who are completely black. The Yemenite Jews are of short stature, mostly dolicocephales, and blonds are not found in this group.

It should be emphasized that no appreciable difference in mortality or morbidity from tuberculosis has been found between the Ashkenazi, Sephardi, and Oriental groups. In striking contrast is the prevalence of tuberculosis among the Yemenite Jews. The high resistance of the first-mentioned groups to tuberculosis is an old and a well-known problem which has received considerable attention. These groups were always cited as an example of a highly immune ethnic group in contradistinction to the marked susceptibility of the non-white races. This well-known fact was confirmed once again by the first published tuberculosis mortality rate in Israel for 1949. In spite of the post-war conditions, of a tre-

[1] From Hadassah Mayer de Rotshild University Hospital, Jerusalem, Israel.

mendous influx of immigrants (the population increased 50 per cent in one and one-half years), and in spite of the fact that Israel was the only country which permitted free immigration of tuberculous patients, the mortality rate in Israel was one of the lowest in the world, i.e., 14.3 per 100,000 for pulmonary tuberculosis and 19.6 per 100,000 for tuberculosis of all forms (9). The older statistics always showed that the tuberculosis mortality rate of Ashkenazi and Sephardi

TABLE 1

TUBERCULOSIS MORTALITY AMONG JEWS AND NON-JEWS LIVING IN THE SAME COUNTRY OR TOWN

AUTHOR	COUNTRY OR TOWN	PERIOD	TUBERCULOSIS MORTALITY*		REMARKS
			CHRISTIANS	JEWS	
1. Bienstok	Petersburg	1905–1914	370	170	
2. Sokolowski	Warsaw	1900–1902	272	144	
3. Thon	Cracov	1896–1900	664	205	
4. Rosenfeld	Lwow	1892–1902	635	306	
5. Proca	Bucarest	1900	387	256	
6. Auerbach	Budapest	1901–1905	392	206	
7. Rosenfeld	Vienna	1901–1903	496	179	
8. Stat. Yahrbuch	Berlin	1905	216	98	
9. Kirchner	Munchen	1901–1908	350	111	
10. Haltrecht	Hesse	1906–1910	225	85	
11. Rosenbaum	London	1900	179	123	
12. Sofer	New York	1884–1890	205	98	White Americans
13. Billings	New York	1884–1890	205	76	White Americans
14. Fishberg	New York	1901–1903	450	180	Irish, Italians
15. Drolet	New York	1918–1921	108	86	
16. McCarthy	United States	1910	210	170	
17. Dublin	New York State	1910	270	105	
18. Dublin	Pennsylvania	1910	177	107	
19. Statistic Office	Warsaw	1921–1932	295	109	
20. Statistic Office	Lodz	1921–1932	334	120	
21. Statistic Office	Bialystok	1921–1932	310	115	
22. Mentchitski	Krim	1926	206	113	306 Tartars
23. Toistivint	Tunis	1895–1900		75	510 Moslems
24. Office d'Hygiene	Tunis	1909–1932	164	86	562 Moslems

* per 100,000

Jews was one-half to one-third that of Christians, and one-fifth to one-seventh that of Moslems living in the same country (table 1).

When the population of an area consists of various ethnic groups, there are always significant relationships between tuberculosis mortality and economic status. In this respect the Jews are an exception (2). The mortality of Jews in various towns was always lower than that of other groups, regardless of economic status. A statistical study of 25,000 Jews in Tunis (18, 29), made during a twenty-four-year period, indicates that the mortality from tuberculosis was one-half that of French and Italian, and one-seventh that of the Moslems, al-

though the standard of living among Tunisian Jews did not differ significantly from that of the Arab masses and was much lower than that of either French or Italians. The same observations apply to the Jewish communities in New York City. There the statistics cover periods which include the difficult years of Jewish mass immigration. Nevertheless, the mortality from tuberculosis among New York Jews in comparison to other ethnic groups is shown in table 2 (4, 11).

These observations do not mean that the mortality of Jews from tuberculosis is independent of environmental factors. On the contrary, this dependence is shown clearly in the records of tuberculosis mortality of Polish and Jewish populations in Warsaw during the first and second World Wars (16, 17).

It is clear from the foregoing that during World War I, when the two populations suffered in the same manner, the mortality from tuberculosis rose in the

TABLE 2

TUBERCULOSIS MORTALITY IN NEW YORK AMONG DIFFERENT ETHNIC GROUPS

AUTHOR	PERIOD	IRISH	NEGROES	GERMANS	AMERICANS	JEWS
Billings	1884–1890	645	531	328	205	76
Drolet	1918–1921	308	398	133	108	86

TABLE 3

TUBERCULOSIS MORTALITY IN WARSAW AMONG POLES AND JEWS DURING THE PERIOD 1910–1942

	1910–1913	1915	1916	1917	1918	1919	1920	1934–1938	1939	1940	1941	1942
Poles	389	450	746	1,150	983	757	396	186	205	377	436	425
Jews	156	200	407	728	512	326	222	71	92	205	434	601

same manner. During World War II, when the Jewish suffering in the Warsaw ghetto was indescribable, the mortality from tuberculosis of the Polish population increased 2.3 times, while the mortality from tuberculosis of the Jewish population increased 8.5 times and became greater than the Polish mortality value. In addition to these figures, it should be emphasized that phthisiologists observed forms of tuberculosis in the Jewish population which they had never formerly seen, i.e., frequent caseous involvement of lymph nodes, massive exudative infiltrations in the lungs, and a greater tendency to miliary spread (20).

This influence of environmental factor was also emphasized by Drolet (12). In his study, it is shown that, as the Jewish community moved from the crowded Lower East Side tenements to a more prosperous section of Manhattan around Mount Sinai Hospital and finally into the Tremont District in the Bronx, which was a comparatively new development in 1923, their tuberculosis death rates went down from 83 per 100,000 to 65 and 52, respectively.

According to Drolet (13), the number of known cases of tuberculosis on January 1, 1952, in three largely Jewish districts of New York City was as

follows: in the Lower East Side, the known cases of tuberculosis per 1,000 residents was 5.84; in the Tremont District in the Bronx, it was much less, namely, 1.56; in the Gravesend District of Brooklyn, which is a more prosperous neighborhood, it was the lowest of any in the city, 0.82.

Morbidity: The significance of the morbidity rate of tuberculosis is perhaps greater than that of the death rate. A constant relationship does not always exist between these two ratios. If under normal conditions the Jewish mortality from tuberculosis is less than the non-Jewish, it cannot be deduced that the morbidity from tuberculosis will be significantly less. Comparative studies between the morbidity of the Jewish and Polish populations may provide a good example. While the Polish mortality from tuberculosis was three times greater than the Jewish, there was not a great difference between the morbidity figures for these two groups (1, 2). There were 1,100 cases of clinical tuberculosis per 100,000 Jews, while for each 100,000 Poles there were 1,300 cases of clinical tuberculosis. It should be noted, however, that the recording of new cases of tuberculosis may again vary considerably from these figures. In 1931, there were 130 new cases of tuberculosis per 100,000 Jews in Warsaw, while there were 300 cases of tuberculosis per 100,000 Poles. This apparent contradiction will be understandable when we consider that Jews are affected with milder clinical forms of the disease and therefore live longer.

The relationship between morbidity from tuberculosis and mortality has been expressed as a coefficient. In 1920 to 1939, this coefficient was 5 for Poles living in Poland and 9 for Jews in Poland. The statistics of MacLennan (23) in 1935 showed a morbidity among the Jewish population in Palestine of 397 and a mortality of 42.6, which resulted in a coefficient of 9.3.

Proof is lacking that the incidence of tuberculosis is decreasing in Israel. The records show that the morbidity incidence is 3 per 1,000 among the old population and from 3 to 9 per 1,000 among the new immigrants (8, 9). The general morbidity rate among Jews in Israel can be estimated as 400 per 100,000 (clinical tuberculosis). The mortality rate for 1949 having been 19.6, the coefficient of morbidity to mortality was 20. When the tuberculosis rate decreased from 42.6 to 19.6, or to 46 per cent of its original value, the morbidity rate remained without change.

According to Edwards and Drolet (14), this same increasing gap has been noticed in the United States. Between 1940 and 1947, the death rate from tuberculosis decreased 27 per cent, while the registration of new cases increased 22 per cent. In 1930 to 1935, Drolet estimated (11) that there were in the United States two new cases reported during a given year for each death, and a total of five cases of clinical tuberculosis. In 1950, Drolet claimed the ratio of ten clinical cases for each death. These observations are similar to those of the present writer.

Tuberculosis Among Yemenite Jews: Official records regarding the morbidity and mortality among different Jewish ethnic groups do not exist. In Israel there is no registration according to the various stocks. Nevertheless, there are data available which throw considerable light upon this problem. While the Yemenite

Jews represent 5 to 6 per cent of the total population, 45 per cent of all beds in the four wards for tuberculous children are occupied by Yemenite children. Among 1,354 children in Tel-Aviv schools who reacted positively to the tuberculin test, Brinberg (5) found 28 children with active tuberculosis, of whom 21 were Yemenites. The tuberculin index was 15.3 per cent among Ashkenazi children, 16.6 per cent among Sephardi, 16.7 per cent in Oriental communities, and 26.4 per cent among Yemenites. While the infection ratio of the Yemenite to Ashkenazi children was 1.7:1, the morbidity ratio was 5:1. The morbidity ratio of Yemenite to Ashkenazi adults was 2.5:1. The mortality ratio is certainly higher. The mortality among Yemenite Jews in the Hashed Camp in Aden in 1947 to 1948 was 350 per 100,000 (7).

In regard to the different forms of tuberculosis noted in Yemenite Jews, one must emphasize that the acute forms of tuberculosis are quite frequent (30). The massive exudative forms so rare in other Jewish groups are not unusual among the Yemenites, and it is therefore frequently possible to guess the stock from which a patient originates by the appearance of his chest roentgenogram. In the military tuberculosis hospital in Safad with 25 per cent Yemenite soldiers, it was amazing to see what extensive pulmonary lesions could develop in a short time. The known symptomatic duration of tuberculosis among the fatal cases averaged 1.7 years in the Yemenite group and 8.3 years in the Ashkenazi group. Before the era of antimicrobial drugs, a one-stage evolution of the disease was frequently observed with persistent fever and a steadily downhill course, which was terminated by death ten to fourteen months after onset. Undoubtedly, the very difficult social and economic conditions under which Yemenite Jews have existed account to a large extent for the high incidence of tuberculosis among them. Under this heading their primitive way of living and the complete absence of hygiene must be considered. But at the same time the North African Jews,[2] mostly Moroccans, who lived under the same poor economic conditions, had the expected morbidity and mortality rate. Their children occupy 8 per cent of the tuberculosis beds, while the Yemenite children occupy 45 per cent.

It is believed that this situation can possibly be explained only if it be assumed that the Yemenite Jews have a diminished ability to develop acquired immunity as a result of infection. An appropriate statement might be that the outcome of tuberculous infection depends, not only upon the circumstances of the individual's life, but also upon certain inborn factors associated with the stock from which he comes (25).

It is not possible to guess even approximately the morbidity from tuberculosis of Yemenite Jews in Yemen. Yemen was almost free of tuberculosis until the Yemenite revolution against Turkey at the beginning of the twentieth century. The military forces which Turkey sent to put down the revolution brought tuberculosis with them. In Yemen there is no medical organization in the accepted sense of the term. The treatment of each disease consists in the burning of

[2] The emigration of North African Jews during the years 1948–1950 numbered 57,700; that of Yemenite Jews, 46,638. The North African Jews constitute from 10 to 12 per cent of the population.

the various parts of the body. The standard of living of Yemenite Jews in Yemen was similar to that of an Arab village in Israel. The Jews did not crowd into large villages but, rather, were peasants or laborers. There was a Jewish tribe by the name of B'nai Haban which wandered with its herds, carrying arms as in the time of patriarchs.

In Yemen there are two centers of tuberculosis, Aden and Sana and their environs; the latter city is the capital. The rest of this mountainous country is free from tuberculosis. In 1913, Much (22) ascertained that almost all of Yemenite Jewish immigrants into Palestine reacted negatively to the tuberculin test. This reaction was positive if they had spent time in Aden before immigration. This writer also stated that a positive tuberculin test in the Yemenite Jews meant active tuberculosis. It seems paradoxical that, while the Jews were considered an example of a group with high resistance to tuberculosis, this particular stock represented a group with remarkably low resistance.

There has been considerable discussion concerning the relative importance of the infection, social environment, and heredity in relation to the course of tuberculosis in a given individual. Calmette (6), for example, who represented the infectionist trend in the development of tuberculosis, maintained that because Jews are an urban element they become more infected in childhood more frequently than in other groups. He suggests that this infection is a sort of vaccination which results in a decreased morbidity and mortality. This idea, however, was no longer tenable when it was shown that the tuberculin index of Jewish children did not exceed that of Polish or Negro children. Moreover, as noted above, the economic and social status does not explain the high resistance of Ashkenazi and Sephardi Jews, just as it does not explain the diminished resistance of Yemenite Jews.

Many authors still maintain that diminished resistance of certain races is the result of natural racial susceptibility. Pinner and Casper (26) have suggested that both the high mortality and the peculiarities of the disease suggest the likelihood of true genotypic differences between Negro and white. Long (21) also states that certain differences in the anatomic character of the tubercle in Negroes from the character of the analogous lesion in whites would seem to have significant hereditary differences. Arnould (3), in a study of tuberculosis in Celtic populations of Brittany, Ireland, Scotland, and Wales, concluded that an important factor in the higher incidence of tuberculosis in the Celts must be attributed to a certain hereditary physico-chemical constitution.

In the tuberculosis of Yemenite Jews, the factor of racial susceptibility (genotypic differences) cannot be used to explain the observations because all Jews have the same racial origin. To be sure, during the course of two thousand years or more,[3] an unknown degree of racial mixture has taken place. But the mixture of Arab blood took place equally in Iraq and Morocco without reducing the resistance of these Jews to tuberculous infection.

The present writer believes that the tuberculosis in Yemenite Jews is a conse-

[3] Some historians assert that the Yemenite Jews belong to the Diaspora which arose after the destruction of the first temple, 586 B. C.

quence of emigration from an agricultural section and open-air life, where tuberculosis was almost unknown, to urban communities where tuberculosis was endemic.

Presumably due to the process of natural selection, the Ashkenazi, Sephardi, and Oriental Jews, who were for centuries exposed to tuberculosis in urban communities, acquired a greater degree of resistance to this infection. The Yemenite Jews, i.e., the section of Jews who lived under desert conditions such as are found in Yemen far from the rest of the people, are now paying the same price as any other group would pay which had been free from previous contact with the tubercle bacillus. Fishberg is correct in stating (15) that there are no races which are more vulnerable to this disease because of phylogenetic peculiarities. Each human group, after exposure to the tubercle bacillus over a period of many generations, acquired a certain degree of immunity. Although the genetic mechanism plays an important role in the dynamics of natural selection, it does not imply transmission of a constant genotype as, for example, skin color or stature. The transmission of a true genotypic factor is seen in the rabbit's resistance to human tubercle bacilli and in its susceptibility to infection with bovine tubercle bacilli. But in man, in whom higher resistance results from a process of natural selection through early death of constitutionally weak or nonresistant family strains in primitive people, it is not proper to speak of natural racial susceptibility by which is meant a constant, definite, transmissible susceptibility.

Certain forms of tuberculosis, for example, massive exudative infiltration, caseation of lymph nodes, and hematogenous spread, are not therefore a peculiarity of the primitive races. In the tragic days of the Warsaw ghetto, these forms of tuberculosis were very common in the Jewish population which was highly resistant until then to tuberculous infection. The fate of the Indians, Negroes, South Sea Islanders, and other groups who were decimated in acute epidemics of tuberculosis in the nineteenth century is an illustration that the high incidence of tuberculosis in primitive peoples is due to their shorter acquaintance with this disease. With the presently available improved facilities, improved methods of diagnosis, isolation technique, antimicrobial drugs, surgical therapy, BCG, and continued improvement of social and economic factors, natural selection plays a much less dramatic role.

SUMMARY

The high resistance of Jewish people to tuberculosis has once more been confirmed by the mortality rate in Israel, which is one of the lowest in the world, despite very difficult economic conditions. The morbidity rate, however, is no less than in other countries. The estimated morbidity-to-mortality ratio is 20, while in pre-war time it was 9. The increase of this coefficient is due to a decrease of the mortality rate, while the morbidity rate remained unchanged. Among the four ethnic Jewish groups which are in Israel, the Yemenite Jews are remarkable for their lack of resistance to tuberculous infection. The high susceptibility to tuberculosis in this group is probably due to its shorter acquaintance with this disease.

SUMARIO

La Tuberculosis entre los Judíos: Mortalidad y Morbidad en Diversos Grupos Etnicos Judíos. Tuberculosis entre los Judíos del Yemen. Factores Etiológicos

La elevada resistencia del pueblo judío a la tuberculosis se ha visto una vez más confirmada por la mortalidad tuberculosa en Israel, que es la más baja del mundo, a pesar de la dificilísima situación económica. Sin embargo, la morbidad no es menor que en otros países. La razón calculada de morbidad-mortalidad es de 20, en tanto que antes de la guerra era de 9. El aumento de ese coeficiente procede de la baja de la mortalidad, mientras que la morbidad ha permanecido inalterada. Entre los cuatro grupos étnicos de judíos que hay en Israel, los yemenitas se distinguen por su falta de resistencia a la infección tuberculosa. La alta susceptibilidad a la tuberculosis en ese grupo se debe probablemente a ser más breve su contacto con la dolencia.

RESUME

La tuberculose chez les Juifs: Mortalité et morbidité parmi les différents groupes ethniques juifs. La tuberculose chez les Juifs originaires du Yemen. Facteurs étiologiques

La résistance à la tuberculose du peuple juif, a été une fois de plus confirmée par le taux de mortalité en Israel, qui est le plus bas du monde entier, en dépit de conditions économiques très difficiles. Le rapport de la morbidité à la mortalité est évalué à 20, tandis que dans la période précédant la guerre il était de 9. L'élévation de ce coefficient est dû à la diminution du taux de mortalité, tandis que le taux de morbidité est demeuré stable. Parmi les quatre groupes ethniques qui sont en Israel, les Juifs du Yémen se signalent par leur manque de résistance à l'infection tuberculeuse. La sensibilité élevée que ce groupe présente pour la tuberculose est probablement due à son exposition assez récente à cette maladie.

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HORNER'S SYNDROME COMPLICATING SURGERY FOR PULMONARY TUBERCULOSIS[1]

A Review of Five Cases

EDWARD J. WELCH

(Received for publication July 30, 1952)

Since Horner's (1) description in 1869, the syndrome that bears his name has been described in a great variety of diseases. Its occurrence as a complication of surgery for pulmonary tuberculosis has also been recorded. The present paper reviews briefly the latter occurrence of the syndrome and reports illustrative cases.

ANATOMY AND PHYSIOLOGY

Although various degrees of Horner's syndrome may be seen in interruptions of the sympathetic pathway in the hypothalamus, midbrain, pons, medulla, and cervical region of the spinal cord, it is not so intense as when due to interruption of the pre- or post-ganglionic cervical sympathetic fibers (2). The preganglionic fibers leave the cord by the anterior roots of the seventh and eighth cervical and first, second, and third thoracic nerves. Most fibers for the pupil leave via the first thoracic segment and enter the first thoracic sympathetic ganglion, which is often fused with the inferior cervical ganglion to form the stellate ganglion. The stellate ganglion normally lies between the base of the transverse process of the seventh cervical vertebra and the neck of the first rib. It is separated from the parietal pleura of the dome of the thoracic cage by the loose connective tissue of the endothoracic fascia. The preganglionic fibers continue on to the mid-cervical and superior cervical ganglions. Synapse takes place in the superior cervical ganglion. The post-ganglionic fibers form the internal carotid nerve which accompanies the internal carotid artery into the skull to make the internal carotid and cavernous plexuses. Vasoconstrictor branches from the cavernous plexus accompany the short ciliary nerve to the eye and orbit. Branches from the carotid plexus traverse the gasserian ganglion and accompany the first division of the trigeminal nerve and its naso-ciliary branch and join the long ciliary nerve to the ciliary plexus, whence they reach the dilator iris, the smooth muscle of the eyelid, and the orbital muscle of Müller.

Bernard (3) in 1852 described the effect of cutting and stimulating the cervical sympathetic pathway in the rabbit. Division of the nerve resulted in constriction of the pupil, injection of the conjunctiva, enophthalmus, hypotonia, and diminution of the size of the eyeball, narrowing of the palpebral aperture, diminution of the size of the naris, flushing and increased warmth of the face. Stimulation of the distal segment of the severed nerve reversed these findings. In 1864, Weir Mitchell, Morehouse, and Keen described for the first time the syndrome in a

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human being, following a gunshot wound of the neck, and attributed the syndrome to injury of the cervical sympathetic pathway (4, 5).

The action of certain drugs on the pupil in Horner's syndrome is of interest. Epinephrine (1:1,000 aqueous solution), when dropped into the conjunctival sac, will not cause dilation of the normal pupil. In Horner's syndrome, if the lesion is in the post-ganglionic (adrenergic) fibers, dilation occurs because denervated smooth muscle becomes sensitive to epinephrine. If, however, the lesion is in the preganglionic (cholinergic) fibers, this action is very slight (6). In addition to the effect on the pupil in the post-ganglionic lesions, elevation of the lid may occur upon instillation of epinephrine into the conjunctival sac.

A 4 per cent solution of cocaine hydrochloride, when instilled into the conjunctival sac of a normal eye, results in dilation of the pupil. The mechanism of action of cocaine has not been exactly determined. It is likely that it stimulates the sympathetic nerve endings in the dilator muscle. The action apparently is not directly on smooth muscle itself, for the action is abolished when paralysis of the cervical sympathetic nerve is present (7).

Atropine (1 per cent solution), which produces dilation of the normal pupil by paralyzing the constrictor muscle of the iris and allowing the unopposed action of the cervical sympathetic to dilate the pupil in a normal eye, is much less effective in the pupil of Horner's syndrome. Horner noted this by comparing the effect of atropine upon the normal and affected eyes of his patients (1).

CLINICAL FINDINGS

In addition to the findings in the eye described by Bernard in lesions of the cervical sympathetic in the rabbit, other aspects have been noted clinically. These include the following homolateral signs: pseudo-ptosis (1) anhidrosis of face and neck (1), dilation of the retinal arteries when flushing of the face is present (1), heterochromia iridis in congenital cases (8), atrophy of the facial muscles (8), vasomotor rhinitis (9), loss of pigment from the iris (10).

Wagener (11) in ninety-four cases of Horner's syndrome found true enophthalmus by measuring with the exophthalmometer in only one case. It is probable that the usual clinical finding of enophthalmus is an optical illusion resulting from the pseudo-ptosis of the upper eyelid.

In man, Jaffe (6) points out that in post-ganglionic lesions, miosis is most marked during the first few hours. Thereafter, the denervated dilator muscle becomes sensitive to circulating epinephrine. He finds that ptosis is a less constant feature. Homolateral facial flushing may be noticed when the patient is at rest, but pallor when the patient is active, due to the effect of circulating epinephrine following the reaction of denervation.

OCCURRENCE IN SURGERY FOR PULMONARY TUBERCULOSIS

Horner's syndrome may result from trauma to the cervical sympathetic system at the time of certain surgical procedures performed for pulmonary tuberculosis. Among these procedures are phrenic exeresis, phrenemphraxis, thoracoplasty,

internal pneumonolysis, and extrapleural dissection in the course of pulmonary resection or in the development of an extrapleural space for pneumothorax.

There have been numerous reports of Horner's syndrome occurring after phrenicectomy. Vaccarezza and associates (12) review cases in the literature and add two of their own occurring after resection of 12 cm. and 6 cm. of the phrenic nerve. They quote Sauerbruch's opinion that Horner's syndrome is due in these cases to avulsion of sympathetic roots (13). The role of anastomotic fibers between the stellate ganglion and phrenic nerve is discussed. Roloff (quoted in 12) reported three cases occurring after phrenicectomy and two after phrenemphraxis; the syndrome was transitory in the latter. De Jong (14) mentions the value of procaine block of an unidentified nerve at the time of operation on the phrenic nerve. In his case what was thought might be an accessory phrenic nerve was thereby demonstrated to be the cervical sympathetic. He also mentions one case of Horner's syndrome occurring at the time of phrenemphraxis. Injury to the cervical sympathetic chain would then appear possible in the course of phrenemphraxis due to one of three causes: the failure to identify the phrenic nerve properly and crushing the cervical sympathetic by mistake; inclusion of both nerves in the clamp; and inadvertent trauma in searching for the phrenic nerve. In phrenic exeresis, avulsion of anastomotic sympathetic fibers would seem the most likely cause.

Horner's syndrome following intrapleural pneumonolysis is less common. Paley (15) describes one case in which the syndrome occurred but disappeared within four months. In Kross' case (16) the syndrome persisted until the time of the patient's death fourteen months after pneumonolysis. Injury of the stellate ganglion or cervical sympathetic fibers directly by the cautery seems unlikely. The occurrence of the syndrome is distinctly rare following this very common surgical procedure. Such direct injury might occur, as Kross suggests, when the cervical sympathetic pathway deviates from its usual course. Zimmerman (17) described Horner's syndrome occurring after section of adhesions at the level of the fourth or fifth dorsal vertebra. Berard (18) describes one case in which the syndrome occurred following the spontaneous rupture of an adhesion. He suggests that traumatic avulsion of sympathetic nerves may thus occur, producing the syndrome. Hanrion and his associates (19) describe four cases in which the syndrome followed intrapleural pneumonolysis and disappeared within six months of its occurrence.

The occurrence of Horner's syndrome in surgical excision of all or part of a lung with extrapleural stripping has been described by Greenwood and Lecos (20). Fourteen of thirty-nine patients who had excisional treatment presented a homolateral Horner's syndrome attributable to the operative procedure. In none of the excised material was sympathetic nervous tissue demonstrated. Injury to the stellate ganglion while developing a plane of cleavage between the parietal pleura and the endothoracic fascia is thought to occur, particularly when dense fibrosis has involved these structures, obliterating the plane of cleavage and making it necessary to develop a deeper plane through the fascia itself. Of the fourteen, seven had persistent findings at subsequent examinations one to fourteen months postoperatively; seven had no residual findings.

In thoracoplasty for pulmonary tuberculosis, Horner's syndrome is distinctly a rare complication. When this operation is combined with Semb apicolysis, however, injury of the stellate ganglion may occur. Kross (16) described this complication in two cases. In each case the pulmonary apex was densely adherent to the neurovascular structures and was dissected free by sharp and blunt dissection until the apex of the lung dropped free. In each case the syndrome was still present at follow-up examination at least a year postoperatively.

CASE REPORTS

Case 1: B. D., a 22-year-old single white female, was admitted to the sanatorium on June 27, 1947, with active tuberculosis in the upper one-third of each lung field. The pupils were equal and reacted to light. The palpebral apertures were not abnormal. Left pneumothorax was induced November 11, 1947.

On January 28, 1948, pneumonolysis was performed. The surgical note read "The thoracoscope was introduced in the fifth interspace in the mid-scapular line. The cautery was introduced in the third interspace in the mid-axillary line. Four band adhesions, one cord adhesion, and a rather thick fleshy band were divided. Most of them suspended the apex at the margin in the region of the second rib posterolaterally. As a result of this there was an excellent drop of the apex. No tubercles were seen. The skin incisions were closed with interrupted silk."

After the operation it was noticed that the patient had a Horner's syndrome on the left and a dry left arm and hand. The findings on the left at examination were apparent enophthalmus, a smaller pupil, pseudo-ptosis, a flushed and warmer left cheek, congestion and swelling of the left middle turbinate, a warm and dry left upper extremity as compared with the right. Both pupils reacted to light and accommodation.

Ephedrine sulfate (0.025 gm. three times daily) relieved somewhat her nasal congestion. There was gradual improvement over a period of many weeks: "enophthalmus," pseudoptosis, congestion of the nose, and flushing of the left cheek disappeared. Perspiration returned to the left arm and hand.

At the last observation (September, 1951), only slight miosis persisted. All other findings had disappeared, and the patient was receiving no sympathicomimetic medication.

Case 2. E. L., a 25-year-old white housewife, entered the sanatorium on August 8, 1942, with active tuberculosis of each lung. On admission, the pupils were equal and reacted to light. No abnormality of the palpebral apertures was noticed.

On September 21, 1942, a phrenic crush was done on the right. The surgical note read "The usual incision was made and the anterior scalene muscle identified. No large phrenic trunk could be found, but there were several small nerve fibers running in the direction of the trunk and in the proper location which were pinched. A long and careful search was made during which the sympathetic chain was identified running along the vertebral column, and some of the lower branches that go to make up the brachial plexus were also seen. The wound was closed with buried sutures in the platysma and subcuticular sutures in the skin."

After the operation, a right Horner's syndrome was noticed. There was a small pupil, pseudo-ptosis, "enophthalmus." There was no facial flush. Over a period of weeks, gradual improvement was noted, and at the time of discharge on August 2, 1943, a miotic pupil was all that remained of the syndrome. The right leaf of the diaphragm showed no motion and a satisfactory rise after the operation. It remained immobile for at least eight months.

Miosis, partial ptosis, and "enophthalmus" persisted until the time of death, Feburary 6, 1946.

Case 3. P. G., a 40-year-old male, was admitted to the sanatorium April 15, 1947, with moderately advanced bilateral pulmonary tuberculosis. The disease was largely fibrocalcific in both upper lung fields but a small cavity had been observed off and on in the second left anterior interspace since 1942. Sputum was intermittently positive for tubercle bacilli. Operation was elected on September 29, 1948. The left thorax was entered through the subperiosteally resected fifth rib. Many fibrous and strandlike adhesions over the apex were divided. A shrunken portion of the left upper lobe, consisting of the apical and subapical segments, contained all of the palpable disease, and these segments were removed.

Postoperatively, miosis, pseudo-ptosis, and facial flushing on the side of the operation were noted. These were present in less marked degree on January 3, 1949. When last seen in September, 1950, there were only slight residual miosis and pseudo-ptosis.

Case 4. A. P., a 36-year-old female, was admitted to the sanatorium on January 10, 1949, with far advanced pulmonary tuberculosis. The patient had had previous left pneumothorax complicated by apical adhesions, all but one of which had been successfully divided in three operations of internal pneumonolysis. On admission, the chest roentgenogram showed a dense left hemithorax due to fluid and probable atelectasis. A bronchopleural fistula and putrid empyema were present but responded to treatment by drainage and chemotherapy. Bronschoscopy revealed concentric narrowing of the left stem bronchus to a diameter of 3 mm.

On April 24, 1949, extrapleural pneumonectomy was performed. "The left fifth rib was resected subperiosteally, exposing a greatly thickened pleura. An extrapleural plane was developed and continued by sharp and blunt dissection up over the apex. The only plane available brought down some shreds of periosteum and intercostal muscle fibers with the thickened pleura. In this plane the upper lobe was completely freed to expose the mediastinum and its contents." The remainder of the surgical note had to do with the ligation and division of the bronchus and great vessels and continuation of the extrapleural dissection over the lower lung field.

After operation, miosis and pseudo-ptosis were noted on the left side and persisted at the last examination (September 27, 1950).

Case 5. M. C., a 20-year-old student nurse, developed an acute tuberculous pneumonia in the upper third of the left lung in May, 1945. This was accompanied by a small homolateral pleural effusion which contained tubercle bacilli. After ten months of bed rest, thoracoplasty was performed in two stages for residual cavitation. At the first stage, the first three ribs were removed and Semb apicolysis was performed. After this stage, left Horner's syndrome was noted. Pseudo-ptosis was marked and the patient could barely open the eye in the first two weeks. There was also dryness of the left side of the face and the left hand.

Slight improvement took place gradually, but at examination on April 23, 1952, there remained moderate pseudo-ptosis and slight miosis.

SUMMARY

Horner's syndrome may occur in the course of operations for pulmonary tuberculosis. In such cases, the syndrome is probably due to direct trauma to the stellate ganglion except in the course of phrenic nerve operations, when direct trauma to the post-ganglionic cervical sympathetic fibers is responsible.

The incidence of the syndrome should be negligible when apicolysis is avoided in the performance of thoracoplasty, when caution is used in identifying the

phrenic nerve at the time of phrenemphraxis, and when extrapleural procedures are kept at an unavoidable minimum. Phrenicectomy and phrenic exeresis have little or no indication now in the management of pulmonary tuberculosis.

The material in the present report should not be interpreted as giving any indication of the incidence of this syndrome as a result of surgery for pulmonary tuberculosis. The cases described here were collected from four hospitals, and no surgeon operated upon more than one of the 5 patients.

SUMARIO

El Síndrome de Horner como Complicación de la Cirugía en la Tuberculosis Pulmonar: Repaso de Cinco Casos

El síndrome de Horner puede presentarse en el transcurso de operaciones ejecutadas por tuberculosis pulmonar. En esos casos, débese probablemente a traumatismo directo del ganglio estrellado (primer ganglio torácico), excepto en las intervenciones en el frénico, en las que la causa radica en traumatismo directo de las fibras simpático-cervicales postganglionares.

La incidencia del síndrome debería ser menospreciable cuando se evita la apicolisis al ejecutar una toracoplastia, cuando se despliega cautela en la identificación del frénico al llevar a cabo una frenendraxis y cuando se limitan los procedimientos extrapleurales al mínimo irreducible. Hoy día son pocas o nulas las indicaciones de la frenicetomía y de la exéresis del frénico en la asistencia de la tuberculosis pulmonar.

No debe interpretarse este trabajo en el sentido de ofrecer la menor indicación de la incidencia de dicho síndrome como consecuencia de la cirugía ejecutada por tuberculosis pulmonar. Los casos descritos fueron compilados de cuatro hospitales, y ningún cirujano operó en más de uno de los cinco.

RESUME

Le syndrome de Horner comme complication de l'intervention chirurgicale dans la tuberculose pulmonaire: Etude de cinq cas

Le syndrome de Horner peut se manifester au cours des interventions pour tuberculose pulmonaire. Dans ce cas, le syndrome est probablement dû à un traumatisme direct sur le ganglion étoilé, sauf dans les interventions sur le nerf phrénique où le traumatisme des filets ganglionnaires postérieurs du sympathique cervical est responsable.

La fréquence de ce syndrome est rare quand l'apicolyse est évitée dans la thoracoplastie, quand le nerf phrénique est soigneusement repéré au moment de l'écrasement du phrénique et quand les procédés extra-pleuraux sont réduits au strict minimum. La phrénicectomie et l'exérèse chirurgicale n'ont que peu ou pas d'indications dans le traitement de la tuberculose pulmonaire.

Le texte de cet article ne doit pas être interprété comme donnant une indication de l'incidence du syndrome de Horner à la suite des interventions chirurgicales pratiquées dans la tuberculose pulmonaire. Les cas décrits ont été réunis dans quatre hôpitaux différents et aucun chirurgien n'a opéré plus d'un seul des 5 cas.

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Notes

EFFECT OF A MINIMAL DOSE OF CORTISONE[1] COMBINED WITH A SUBEFFECTIVE DOSE OF DIHYDROSTREPTOMYCIN ON EXPERIMENTAL GUINEA PIG TUBERCULOSIS

In previous studies[2,3] it has been demonstrated that cortisone exerts a deleterious effect on experimental tuberculosis. This finding has now been confirmed in clinical experience[3], but it has been maintained that the doses used in animal experiments were in excess of those required for clinical effectiveness.

In a previous study[4] it was determined that the granulation tissue response (wound healing), inflammation, and spleen size were all affected at the same minimal dose. Based on these considerations, the effect of a minimal cortisone dose on experimental tuberculosis modified by concurrent treatment with a subeffective dose of dihydrostreptomycin was studied.

Forty-five tuberculin-negative female guinea pigs weighing 500 to 575 gm. were divided into three groups of 15 each. Infection was accomplished by subcutaneous injection over the sternum of 0.1 mg. (dry weight) of *M. tuberculosis* (H37Rv strain) grown on Petrik's[5] modification of Löwenstein's medium. Fourteen days after infection each animal was tuberculin tested with 0.1 ml. of 5 per cent Old Tuberculin and all were found to give a positive reaction. Treatment was started two days later (sixteenth postinfection day).

The materials administered to the various groups were:

1. Controls: buffered suspending diluent only.
2. Cortisone, 0.25 mg. per animal daily, and dihydrostreptomycin hydrochloride, 2 mg. dihydrostreptomycin base per animal daily.
3. Dihydrostreptomycin hydrochloride, 2 mg. dihydrostreptomycin base per animal daily.

Treatment was continued for thirty days. Animals were sacrificed and evaluation of the extent of tuberculosis was made on the basis of gross and microscopic examination of the degree and character of involvement of the infection site, regional lymph nodes, lungs, liver, and spleen. The findings in each animal were recorded on a point evaluation system assigning numerical values as follows:

0 = No gross or microscopic evidence of tuberculosis.
1 = Minimal to moderate involvement based on characteristic infiltration, degree of caseation, and microscopic evidence of healing.
2 = Extensive involvement with little or no evidence of healing.

A total value of 10 (2 for each of the 5 prior mentioned sites examined) represented maximal tuberculosis.

[1] The cortisone used in this study was generously supplied by Merck and Company, Rahway, New Jersey.

[2] Spain, D. M., and Molomut, N.: Am. Rev. Tuberc., 1950, *62*, 337.

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Gross and microscopic examination of the above-treated experimental groups revealed the following comparative degree of tuberculous involvement:

TABLE 1

GROUP AND TREATMENT	NUMBER OF ANIMALS	TOTAL NUMERICAL EVALUATION OF TUBERCULOSIS	
		Average	*Range*
Control	15	8.0	5–9
Cortisone plus dihydrostreptomycin	15	6.1	4–8
Dihydrostreptomycin	15	4.2	1–7

The cortisone dose administered per animal was equivalent on a weight basis to 25 mg. per 50 kg. of human weight, which is below the usual clinical maintenance dose.

In summary: Cortisone administered in doses lower than comparable daily maintenance doses in humans was found to have a deleterious effect on experimental tuberculosis in guinea pigs.

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July 25, 1952

A NOTE ON THE pH OF TUBERCULOUS EMPYEMA[1]

The impression is gained from the literature that the fluid of tuberculous empyema is acid in reaction. In the past few years this presumed acidity has been incriminated as the probable cause of the ineffectiveness of intrapleural streptomycin in the treatment of this complication. Hinshaw, Feldman, and Pfuetze,[2] commenting on this poor therapeutic response to streptomycin, state: "... This may be due to the fact that the pus of tuberculous empyema is usually acid in reaction." Freedlander and French[3] remark: "Streptomycin is ineffective in empyemata, which are usually acid in reaction," and Kolmer[4] expresses a similar opinion. Recently, Staines and Cardenas,[5] working on this assumption, reported favorable results in the treatment of tuberculous empyema with streptomycin plus alkalinization of the pleural cavity.

A review of the literature, however, discloses very few data on the pH of tuberculous empyema fluid; the little work that has been done indicates that such fluid is more likely to be alkaline. In 1928, Nedelkovitch[6] reported that the pH reactions of ten exudates from cases of tuberculous pleurisy and peritonitis varied from 7.1 to 7.8. His results may not be dependable because the fluids had been stored at room temperature for one to three months before their reactions were determined. Pinner and Moeske[7] studied the physical and chemical characteristics of thirty-two pleural effusions in nineteen patients. Tubercle bacilli were present in all but four of these effusions. They found the average pH was 7.5, with a range of 6.8 to 8.0. The only grossly purulent fluid studied had a pH of 7.6. Their determinations were not electrometrically corrected, and it would appear from their other data that the pH determinations were 0.3 units too high. Making the appropriate correction would still leave the average pH alkaline. Pinner and Moeske also quote the work of Schade and Claussen,[8] who reported in 1925 that pleural exudates had a pH of 6.17 to 7.30. Finally, Canova and Agnelo[9] report that in thirty-seven determinations on eighteen cases of tuberculous empyema the pH was alkaline in all but two instances. In these two, the pH was 7.0 and 6.8. They found that the more purulent fluids tended to have a lower pH.

There thus appears to be disagreement between present concepts and the small amount of experimental work available. Most of the observations were made many years ago and without the benefit of the more accurate methods now available for the determination of hydrogen ion concentration. Because of this, and because of the theoretical implications with regard to antimicrobial therapy, it was believed that a re-study of the subject was indicated.

[1] Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the results of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

[2] Hinshaw, H. C., Feldman, W. H., and Pfuetze, K. H.: J.A.M.A., 1946, *132*, 778.

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[5] Staines, E., and Cardenas, C.: J. Thoracic Surg., 1950, *19*, 891.

[6] Nedelkovitch, Y.: Compt. rend. Soc. de biol., 1928, *99*, 579.

[7] Pinner, M., and Moeske, G.: Am. Rev. Tuberc., 1930, *22*, 121.

[8] Schade and Claussen: Beitr. z. Klin. Tuberk., 1925, *62*, 300, cited by Pinner and Moeske.

[9] Canova, S., and Agnello, V.: Ann. Inst. Carlo Forlanini, 1939, *5*, 232.

Infected tuberculous pleural fluids from patients were studied, and the pH was determined with a Beckman glass electrode apparatus. The determination was usually carried out a few minutes after the fluid was withdrawn. Several duplicate determinations indicated that the values were not affected by keeping the fluid under oil until the determinations were carried out, nor were the values affected if there was a delay of as long as two hours after aspiration.

All but two of the patients were male veterans from this institution. Through the kindness of Dr. Paul Dufault, two specimens of purulent fluid were obtained from the Rutland State Sanatorium; one of these was from a female patient.

There is much difference of opinion as to what constitutes an "empyema." Some regard any pleural fluid from which tubercle bacilli may be grown as empyema. Others

TABLE 1

RESULTS OF pH DETERMINATIONS OF 11 TUBERCULOUS PLEURAL FLUIDS

NUMBER	PATIENT	GROSS APPEARANCE	TUBERCLE BACILLI DEMONSTRATED BY	pH
1.	R. T.	Serofibrinous	Culture	7.5
2.	J. S.	Serofibrinous	Culture	7.4
3.	J. K.	Serofibrinous	Culture	7.5
4.	L. F.	Serofibrinous	Culture	7.4
5.	L. McG.	Serofibrinous	Culture	7.3
6.	G. N.	Serofibrinous	Smear	7.2
Average of 6 serofibrinous fluids				7.4
7.	A. C.	Purulent	Smear	7.3
8.	J. L.	Purulent	Smear	7.4
9.	A. MacN.	Purulent	Smear	7.5
10.	E. L.	Purulent	Smear	6.6
11.	L. M.	Purulent	Smear	7.2
Average of 5 purulent fluids				7.2
Average of 11 fluids				7.3

feel bacteria should be sufficiently numerous to be visible on direct smear, while a third group insists on the presence of frank pus before an effusion may be regarded as an empyema. This is largely a matter of definition, and any concept is acceptable as long as it is clearly defined.

The present study was conducted with fluids which were positive for *M. tuberculosis* on culture. In all cases, cultures for other microorganisms were negative. Information concerning the gross appearance and bacteriology of the fluid is given in the table, however, so that those who adhere to stricter definitions of empyema may also draw conclusions, although from a smaller number of cases.

The results given in the table indicate that in all cases except one the fluid studied was alkaline. The average pH of all eleven fluids was 7.3. The average of the five frankly purulent fluids was 7.2.

The pH of tuberculous empyema fluid is now of more than academic significance, since

it has been demonstrated repeatedly[10-16] that the effectiveness of streptomycin decreases as the medium becomes more acid. Relative effectiveness appears to be present experimentally at pH 7.0. Unfortunately, all of these studies were performed with organisms other than *M. tuberculosis*. The only study found in which the tubercle bacillus was the test organism was that of Hurwitz and Miller.[16] These workers found that a sensitive strain of tubercle bacillus did not grow in the presence of 1 γ or more of streptomycin per ml. at pH 6.0, 7.0, or 8.0. One strain, resistant at pH 6.5, was somewhat sensitive at pH 7.0 and fairly sensitive at pH 7.4. This would suggest that the pH of tuberculous empyema as reported in this paper is within effective ranges for the action of streptomycin on tubercle bacilli. In these studies just cited, however, a wetting agent was present in the medium and this enhanced the activity of the streptomycin in some concentrations at least. More work is necessary before the accurate pH range in which streptomycin is effective upon the tubercle bacillus will be known.

From the evidence available, however, it would appear that an unfavorable pH does not account for the ineffectiveness of intrapleural streptomycin in tuberculous empyema. Other factors probably play a role. Here, it is of interest to recall the work of Penington[17] which was reported in 1939. He found that he could not reproduce experimentally a purulent tuberculous empyema solely by the intrapleural injection of tubercle bacilli in sensitized animals. Under those conditions, only serous effusions appeared. Only when caseous material was permitted to gain access to the pleural space of sensitized animals did purulent empyema result. This suggests that tuberculous empyema is a reaction to other factors than merely tubercle bacilli; if this hypothesis is correct, one could not expect too much from a drug that acted only upon the bacilli present.

In summary: The pH of eleven tuberculous fluids was measured with a glass electrode. In only one case was the pH acid. The pH of the remaining fluids varied from 7.2 to 7.5. The average for the whole group was 7.3. In five cases of frankly purulent fluid, all with acid-fast bacilli demonstrable on smear, the average pH was 7.2. While the effective pH range for the action of streptomycin on tubercle bacilli is not accurately known, it appears from the available studies that the pH of tuberculous empyemas is not unfavorable to the action of streptomycin. It would appear that the other factors are present to account for the ineffectiveness of streptomycin in tuberculous empyema.

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July 30, 1952

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INCIDENCE OF BACTERIAL RESISTANCE ENCOUNTERED WITH TUBERCULOSIS CHEMOTHERAPY REGIMENS EMPLOYING ISONIAZID ALONE AND IN COMBINATION WITH INTERMITTENT STREPTOMYCIN

Numerous investigators are reporting increased resistance to isoniazid in tubercle bacilli isolated from patients who receive this drug alone. Although there is insufficient evidence to correlate loss of clinical response with any exact level of isoniazid resistance, experience with other antituberculous drugs would indicate that the development of a

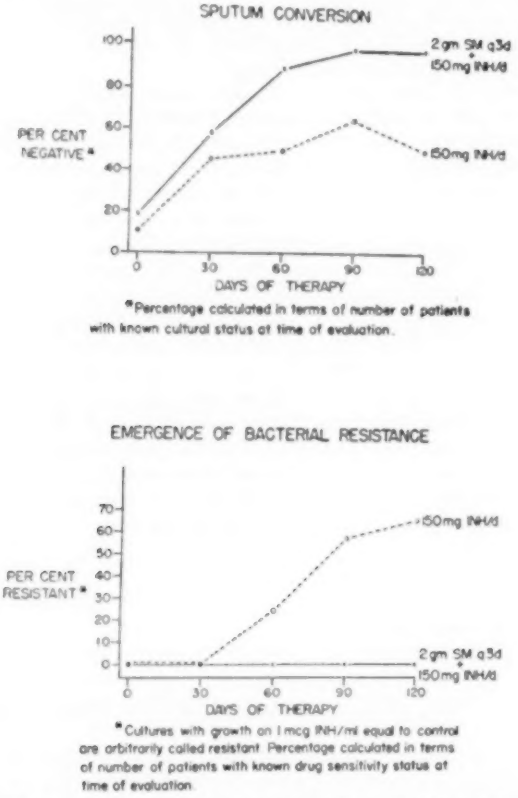

FIG. 1. Bacteriologic evaluation of isoniazid and isoniazid-streptomycin regimens. Preliminary report based on analysis prepared on September 4, 1952.

several-fold increase in bacterial resistance may limit the therapeutic effectiveness of this new agent. Knowledge of other combined drug regimens suggests that the administration of streptomycin or other antituberculous agents with isoniazid may delay the emergence of bacterial resistance to both drugs. To date, however, there have been few published data to substantiate this possibility.

At the Colorado Trudeau Society Meeting at Stead's Ranch, Estes Park, Colorado,

September 6, 1952, the Research Group at Fitzsimons Army Hospital presented a preliminary report on its experience with tuberculosis chemotherapy regimens employing isoniazid alone and in combination with intermittent streptomycin. The bacteriologic data from that report are reproduced here in both graphic and tabular form. In these

TABLE 1

BACTERIOLOGIC EVALUATION OF ISONIAZID AND ISONIAZID-STREPTOMYCIN REGIMENS

(Preliminary Report Based on Analysis Prepared September 4, 1952)

150 Mg. of Isoniazid Daily for 120 Days

	DAYS OF THERAPY					
	0	30	60	90	120	150
Positive						
Susceptible	62	33	19	6	4	0
Resistant*	0	0	6	8	8	0
Pending	0	5	6	1	6	5
Negative	8	31	30	28	18	11
Total	70	69	61	43	36	16

2.0 Gm. of Streptomycin Every Third Day plus 150 Mg. of Isoniazid Daily, Both for 120 Days

	DAYS OF THERAPY					
	0	30	60	90	120	150
Positive						
Susceptible	43	22	5	0	0	0
Resistant*	0	0	0	0	0	0
Pending	0	0	0	1	1	0
Negative	10	31	47	51	35	16
Total	53	53	52	52	36	16

* Drug susceptibility studies were performed on all positive cultures using American Trudeau Society medium containing 0, 0.2, 1, and 5γ of isoniazid or 0, 1, 10, and 100γ of streptomycin per ml. Cultures showing growth on 1γ of isoniazid or 10γ of streptomycin per ml. equal to the control were arbitrarily called resistant. Cultures from all patients were positive and susceptible to isoniazid (no growth or a few colonies on 0.2γ of isoniazid per ml.) prior to initiation of drug therapy.

series of patients, the emergence of bacterial resistance during daily isoniazid therapy appears to be markedly delayed by the concomitant administration of intermittent streptomycin.

RESEARCH AND DEVELOPMENT BRANCH
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September 15, 1952

CONTROL STUDY OF COMPARATIVE EFFICACY OF ISONIAZID, STREPTOMYCIN-ISONIAZID, AND STREPTOMYCIN-PARA-AMINOSALICYLIC ACID IN PULMONARY TUBERCULOSIS THERAPY

II. Report on Twenty-Week Observations on 390 Patients with Streptomycin-Susceptible Infections

Only prolonged clinical observation and more adequate data on bacterial resistance can answer the question of the long-term usefulness of isoniazid in tuberculosis therapy. Meanwhile, speculation is inevitable as immediate decisions concerning the use of isoniazid confront physicians responsible for the care of tuberculous patients. For these pragmatic decisions, the results of even relatively short periods of observation from control studies involving sizable groups of patients should prove useful.

In April, 1952, the directors of twenty-two tuberculosis hospitals[1] met, set up a central coordinating office in the Public Health Service, Federal Security Agency, and agreed to pool their resources in a large-scale cooperative clinical investigation[2] designed to compare the merits of isoniazid alone, isoniazid in combination with streptomycin, and streptomycin with para-aminosalicylic acid (PAS) in the treatment of 1,500 patients with pulmonary tuberculosis.

Very briefly, the plan of investigation was as follows:

Each clinical investigator selected patients whom he considered suitable for the study and sent certain basic clinical information about each of them to the central office. From April through July, 1952, patients were admitted each week and assigned in the central office to one of the three regimens according to a strict system of chance allocation. According to the study plan, therapy would be carried out uninterruptedly for a period of forty weeks, during which time uniform observations would be made and reported on all patients at regular four-week intervals. The three drug regimens were:

Streptomycin-PAS: 1 gm. of streptomycin twice weekly plus 10 to 12 gm. of PAS daily
Streptomycin-Isoniazid: 1 gm. of streptomycin twice weekly plus 150 to 300 mg. of isoniazid daily
Isoniazid: 150 to 300 mg. daily

A preliminary note on the results of twelve-week observations on 526 patients published in the November, 1952, issue of the REVIEW showed isoniazid alone or in combination with streptomycin to be fully as effective as streptomycin with para-aminosalicylic acid. The results of twenty weeks of observation are now available for 390 patients with streptomycin-susceptible infections. In view of the current variance of medical opinion, it appears appropriate to publish at this time summary results on this group observed longest while proceeding with a more detailed analysis on the larger groups.

The present comparison of the three drug regimens after twenty weeks of treatment has been restricted to patients who could be considered capable of responding to streptomycin and PAS, i.e., having streptomycin-susceptible bacilli at the beginning of the study.[3]

[1] The investigators were enumerated in the November, 1952, issue of the REVIEW, page 636.

[2] The isoniazid for this investigation was generously supplied by E. R. Squibb & Sons as Nydrazid.

[3] Determinations were made by the indirect culture method by Mr. William Steenken, Jr. in the Trudeau Laboratory. Cultures were considered sensitive to streptomycin when growth in the 10γ per cc. concentration of streptomycin was less than the four plus growth in the control at five weeks.

A few patients whose pretreatment cultures were negative for *M. tuberculosis* or contaminated have been included because they had received less than 100 gm. of streptomycin prior to the study.

As an indication of the success of the initial randomization, the group of 390 distributes itself about equally between the three treatment regimens, 133 patients received streptomycin plus PAS; 123, streptomycin plus isoniazid; and 134, isoniazid alone. The three groups of patients appeared at selection to have a similar distribution of severity of disease and were comparable with respect to such factors as age, race, and sex. The great

TABLE 1

PERCENTAGE DISTRIBUTION OF ROENTGENOGRAPHIC CHANGE IN 390 PATIENTS WITH STREPTOMYCIN-SUSCEPTIBLE INFECTIONS

	CHANGE FROM BEGINNING OF TREATMENT								
	Total per cent	Improvement			NO CHANGE	Deterioration			DEATH
		MARKED	MODERATE	SLIGHT		SLIGHT	MODERATE	MARKED	
Streptomycin plus PAS									
4 weeks	100.0	0.3	2.3	24.0	69.8	2.8	0.8	—	—
8 weeks	100.0	0.8	6.8	33.9	50.8	2.5	3.3	0.3	1.6
12 weeks	100.0	2.0	15.0	39.2	33.7	4.6	3.5	0.3	1.7
16 weeks	100.0	7.0	19.1	33.4	28.1	3.8	5.6	1.2	1.8
20 weeks	100.0	11.0	20.7	34.2	20.7	4.6	4.6	2.4	1.8
Streptomycin plus Isoniazid									
4 weeks	100.0	—	6.1	28.5	61.7	2.5	0.6	0.6	—
8 weeks	100.0	2.0	17.8	33.1	39.8	4.2	2.3	—	0.8
12 weeks	100.0	4.3	27.4	31.4	27.4	5.2	1.7	0.9	1.7
16 weeks	100.0	12.5	28.9	29.8	19.5	3.5	2.6	0.6	2.6
20 weeks	100.0	19.6	29.4	23.2	19.6	2.4	2.4	0.6	2.8
Isoniazid									
4 weeks	100.0	0.5	4.8	31.3	58.1	4.0	0.8	0.5	—
8 weeks	100.0	1.8	15.9	36.6	42.9	2.3	—	0.5	—
12 weeks	100.0	6.5	23.2	33.3	29.5	4.4	2.1	1.0	—
16 weeks	100.0	8.8	29.9	26.8	24.9	4.6	3.6	1.4	—
20 weeks	100.0	16.5	27.7	22.4	23.0	4.2	4.8	1.4	—

majority (68 per cent) of the patients in this group had moderately or far advanced cavitary disease, a small group (25 per cent) had advanced disease without cavity, and a few (7 per cent) had disease of only minimal extent.

By the end of the twentieth week, 46 cases in this group had deviated from prescribed chemotherapy. Departure from the hospital interrupted the treatment of 14 streptomycin-PAS, 10 streptomycin-isoniazid, and 12 isoniazid patients. Four streptomycin-PAS patients showed intolerance of both streptomycin and PAS, and 3 could not tolerate PAS. One streptomycin-isoniazid patient could not tolerate isoniazid. Critical worsening resulted in a change of chemotherapy for one isoniazid patient after sixteen weeks of treatment. One streptomycin-PAS patient refused the prescribed chemotherapy. For this preliminary analysis, these cases have been included in the tabulations for report periods

preceding the interruption. Despite the interruption, an attempt is being made to keep these cases under observation for inclusion in future analyses, recognizing that certain types of deviations must be considered as treatment failures.

Five deaths occurred among the 390 patients during the twenty weeks of observation; 2 in the streptomycin-PAS group, and 3 in the streptomycin-isoniazid group. The 2 streptomycin-PAS patients died of tuberculosis. In the streptomycin-isoniazid group, one died of tuberculosis, one of cerebral hemorrhage, and one of myocardial infarction.

Change in Roentgenographic Appearance

Rigorous precautions were designed in the planning and execution of the roentgenographic evaluation conference of the clinical investigators to produce objective data on roentgenographic change. A system of random allocation of cases to "readers" provided that: each case was reviewed independently by three "readers"; no physician evaluated any cases from his own hospital; each "reader" reviewed an equal number of cases in each treatment group without knowing the identity of the patient, the hospital, or the treatment regimen. The distribution of the resulting 1,170 opinions of roentgenographic change between selection and subsequent periods is presented in detail in table 1 for each regimen.

With the passage of time, an increasing number of patients in all three groups have shown change from their status at the beginning of treatment, ranging from marked improvement in some to death in others. The major movement in each group, however, was in the direction of improvement. Deterioration of any degree at the end of twenty weeks appeared in only 13.4 per cent of streptomycin-PAS, 8.2 per cent of the streptomycin-isoniazid, and 10.4 per cent of the isoniazid group.

Counting improvement of any degree, the proportion of improved cases was very similar at twenty weeks in the three groups; 65.9 per cent of the streptomycin-PAS group; 72.2 per cent of the streptomycin-isoniazid group; and 66.6 per cent of the isoniazid group. If, however, only moderate or marked improvement is considered as a significant change, sharp differences appear. Only 31.7 per cent of the streptomycin-PAS group were classified as improved in contrast to 49.0 per cent of the streptomycin-isoniazid group and 44.2 per cent of the isoniazid group. Summation of the proportions in table 1 showing marked or moderate improvement at each report period produces the following comparison:

REGIMEN	WEEKS OF TREATMENT				
	4	8	12	16	20
Streptomycin-PAS	2.6	7.6	17.0	26.1	31.7
Streptomycin-Isoniazid	6.1	19.8	31.7	41.4	49.0
Isoniazid	5.3	17.7	29.7	38.7	44.2

In all three groups, the proportion of significantly improved patients increases at each report period. However, at no point in time were the most favorable results achieved with streptomycin and PAS, and from the eighth through the twentieth week of treatment the proportion of markedly or moderately improved patients was considerably higher in the two groups receiving isoniazid.

Some workers have reported a high frequency of relapse among patients receiving isoniazid, paralleling the reported emergence of isoniazid-resistant bacilli. While table 1 does not show directly movement of cases between classifications in different periods, the

progressively upward trend of the proportion improved provides indirect evidence that roentgenographic relapses are not occurring with great frequency in any group.

Although the material is not large, this point has been examined more directly by comparing each twelfth-week judgment of marked or moderate roentgenographic improvement with the comparable twentieth-week judgment on the same case by the same "reader." For this simple comparison, roentgenographic relapse is defined as marked or moderate improvement in the twelfth week of treatment followed by less than moderate improvement in the twentieth week. On this basis, a relapse rate of 10.5 per cent was found in the streptomycin-PAS group, 7.1 per cent in the streptomycin-isoniazid group, and 11.7 per cent in the isoniazid group. In the opinion of the present writers, this probably reflects the variable course of the disease rather than any real differences among the three regimens.

Certain speculations regarding potential synergistic or antagonistic effects of a combination of streptomycin and isoniazid may be permissible. Para-aminosalicylic acid is generally regarded as prolonging rather than materially increasing the therapeutic effect of streptomycin. Therefore, the results achieved with streptomycin and PAS may be considered as representing chiefly the effect of streptomycin. Comparison of the data on the three regimens indicates that the effect of a combination of streptomycin and isoniazid is not as great as would be expected by a simple summation of the effect which the two drugs produce separately. This could be considered evidence of the absence of synergism. Moreover, the finding that results achieved with isoniazid and streptomycin combined are very little higher than with isoniazid alone admits of several possibilities: that isoniazid may interfere with the action of streptomycin; that streptomycin may interfere with the action of isoniazid; or that a mutual interference may exist. The explanation may actually be much simpler. The limit on the number of patients who improve in any given period of time may be imposed by the nature of the disease in the patients under investigation.

Change in Sputum, Fever, and Body Weight

Observations on bacteriologic studies, amount of sputum, fever, and body weight have been grossly classified for the present report simply as "positive" or "negative" sputum smears, copious or less-than-copious amounts of sputum, febrile or afebrile (less than 99°F.), normal or underweight (more than 10 per cent below height-weight standard). The proportion of patients in each group who were in an unfavorable condition with respect to each of these signs at the time of selection and after each four-week period of therapy is shown in table 2.

During twenty weeks of treatment, the proportion of patients with sputum positive for tubercle bacilli decreased markedly on all three regimens. However, small increases may be noted for the streptomycin-isoniazid group in the twentieth week; and, for the isoniazid only group, in the sixteenth and twentieth weeks. While not statistically significant, these increases may conceivably mark the beginning of a trend related to the emergence of isoniazid-resistant organisms.

Twenty weeks' treatment with streptomycin and PAS produced no reduction in the proportion of cases with copious sputum although decreases occurred with the use of the two regimens containing isoniazid.

After twenty weeks of treatment, approximately 10 per cent of each group remained febrile. It is difficult to assess the relative effect of the three drug regimens in reducing fever because the majority of all patients were afebrile at selection and because differences existed among the groups at the beginning of treatment.

The data on changes in body weight have been summarized by comparing the pro-

TABLE 2

PROPORTION OF 390 PATIENTS WITH STREPTOMYCIN-SUSCEPTIBLE INFECTIONS IN UNFAVORABLE CLINICAL CONDITION

	STREPTOMYCIN-PAS	STREPTOMYCIN-ISONIAZID	ISONIAZID
Number of cases	133	123	134
Per Cent Bacteriologically "Positive"*			
Selection	67.6	70.7	62.7
4 weeks	50.4	36.4	33.1
8 weeks	45.0	31.9	27.3
12 weeks	39.3	26.7	25.6
16 weeks	34.2	17.4	28.4
20 weeks	34.5	21.4	29.8
Per Cent with Copious Sputum			
Selection	19.6	18.7	20.1
4 weeks	22.5	20.5	18.8
8 weeks	25.4	21.0	25.8
12 weeks	21.4	15.5	16.3
16 weeks	21.3	8.7	15.4
20 weeks	23.6	13.4	14.9
Per Cent Febrile†			
Selection	15.8	26.0	20.9
4 weeks	12.4	8.2	12.1
8 weeks	18.0	10.9	14.4
12 weeks	14.5	10.3	10.9
16 weeks	9.7	7.8	17.1
20 weeks	10.9	10.7	9.9
Per Cent Underweight‡			
Selection	46.6	48.0	48.5
4 weeks	42.6	46.3	40.9
8 weeks	41.0	41.2	39.7
12 weeks	42.7	40.0	35.2
16 weeks	39.0	38.3	32.5
20 weeks	38.2	34.2	30.8

* Based on microscopic examination of sputum smears; reports on cultures planted concurrently not yet available.

† Median of highest oral temperature for five days: febrile 99.0°F. and above.

‡ Minus deviation of more than 10 per cent from standard height-weight values.

portion of the members of each group who were at least ten per cent underweight at each report period. In all groups, this proportion decreased throughout treatment from slightly less than half at selection to approximately one-third at twenty weeks.

In summary: Comparison of the results of twenty weeks treatment of 390 patients with streptomycin-susceptible infections indicates a significant superiority in roentgenographic

improvement in patients who received isoniazid alone or in combination with streptomycin. By clinical and laboratory comparisons, the differences between the isoniazid regimens and streptomycin-PAS are less marked. In this cooperative study, rigidly controlled to eliminate bias both in the assignment of therapy and the evaluation of results, isoniazid appears, at the least, an extremely effective antituberculous agent for short-term therapy.

DIVISION OF CHRONIC DISEASE AND TUBERCULOSIS
PUBLIC HEALTH SERVICE
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November 18, 1952

American Trudeau Society

Medical Section of the National Tuberculosis Association

The Award of the Trudeau Medal for 1952

The Trudeau Medal for 1952 was awarded to Dr. J. Burns Amberson at the annual meeting of the National Tuberculosis Association. The presentation was made by Dr. John Barnwell as follows:

Dr. Barnwell: Last year, upon the occasion of his election to the honorary medical society, Alpha Omega Alpha, Alan Gregg, vice-president of the Rockefeller Foundation submitted "a few reflections on the early recognition of early ability," two of which follow:

> Since "you have most of your students the same age, the academic rewards . . . go to those who are uncommonly bright *for their age*. In other words you have rewarded precocity, which may or may not be the precursor of later ability. So, in effect, you have unwittingly belittled man's cardinal education capital—time to mature." He concluded with "a plea for more attention to the fact that being a good student is not as interesting as forever becoming one more completely." I take this last remark as my text for tonight's Trudeau award: "being a good student is not as interesting as forever becoming one more completely."

With this in mind I tried to find out just how "precocious" tonight's medalist was. He took the standard "Latin-Scientific" course leading to the B.A. degree. The lowest grade he received in college was in "General Chemistry," and that was his only "B." The professor of physics thought him the best of the elective students in that subject. The president reported him "a good student and a man of ability." The professor of romance languages wrote the medical school of his choice: "I admit he needs more French but his foundation is so excellent that I feel very confident he can meet your requirements."

So, with a deficiency in French he entered a highly competitive medical class of 88 students, at least a half dozen of whom are now full professors scattered from coast to coast. Where he stood in that class is still a secret with the medical school, but it is admitted to be high. He received his highest grades in gynecology, but so did the rest of his class.

I do not choose to disclose his identity by a recitation of his well-known honors recorded in standard biographical directories. I do not presume to give you my own evaluation of his most important contributions. From the moment I saw the first vote of your selection committee last September, I realized that whoever presented this year's medal would be well advised to let the medalist speak for himself through his highly quotable works. When your president decided that I should be made the poor mouthpiece of your Association in this presentation, I reviewed the medalist's publications for this purpose. Lest you miss some recent excitement, I even stole a review of the files at the National Institutes of Health and elsewhere for his most recent progress reports on research now under way.

Rather than take you on a hasty guided tour through all his writings to show you that "forever becoming a good student more completely" is characteristic of this year's winner, I prefer to read you abstracts from just one. I shall let you hear our medalist plan

and carry out a trial of a new drug, collect his evidence and assess it. I shall let him tell the story in his own words, which I now quote:—

"CLINICAL TRIAL OF [A DRUG TREATMENT] IN PULMONARY TUBERCULOSIS

". . . published the results of his study, and made claims that the substance has a specifically curative effect on tuberculosis. He believed that the drug permeates tuberculous lesions and thus kills many, if not all, of the offending bacilli. The resulting reactions . . . were interpreted as being due mainly to the liberation of toxins from the disintegrated bacilli and, therefore, as being analogous to tuberculin reactions. The evidence was obtained from the observation of the action of the chemical compound on living cultures of tubercle bacilli, on the treatment of tuberculosis induced experimentally in goats, calves, monkeys and guinea pigs, and on the treatment of tuberculosis in man by various . . . clinicians.

"An examination of some of the clinical reports does not seem to justify all the conclusions that have been drawn either for or against the drug. Many so-called control cases do not deserve such a designation, and various interpretations of clinical observations are open to question. It is difficult, indeed, in appraising a therapeutic agent for tuberculosis, to distinguish natural fluctuations of the disease from those induced by the substance or procedure under trial. The follow-up of large groups of cases during a period of at least five years after treatment usually yields valuable, if limited, information provided there is not too much disparity in the size of comparable groups. Another method is an intensive study of smaller, carefully selected, and closely comparable groups of cases, according to a prearranged plan. This also is satisfactory for limited purposes but requires special facilities and personnel. Neither of these methods has been applied very rigidly in the case of [the drug now under consideration].

"PLAN FOR CLINICAL TRIAL

"The following plan, embodying what we consider to be the minimum of clinical, laboratory and X-ray observations sufficient to warrant any reasonable conclusion from such a study, was adopted before work was started.

"It was decided to start with a group of patients in good general condition, who would, therefore, not be likely to suffer ill effects from the drug [Here I omit his other criteria for selection].

"Preliminary selections having been made, the patients were assembled, the treatment was explained (except that no mention was made of a control group), and those who so desired were asked to volunteer. An ample number expressed their willingness to accept treatment, and were then given complete examinations. . . . The 24 patients finally chosen were considered to represent exceptionally good subjects for the treatment.

"On the basis of clinical, X-ray and laboratory findings, the 24 patients were then divided into two approximately comparable groups of 12 each. The cases were individually matched, one with another, in making this division. Obviously, the matching could not be precise, but it was as close as possible, each patient having previously been studied independently by two of us. Then, by a flip of the coin, one group became identified as group I (those which were treated) and the other as group II (control). The members of the separate groups were known only to the nurse in charge of the ward and to two of us. The patients themselves were not aware of any distinction in the treatment administered.

"*Method of Observation:* The clinical status of most of the 24 patients was well known from their preceding course in the [hospital]. However, in order to observe conditions more closely, the patients were all put to bed for a month prior to start-

ing any medication. During this month, the data mentioned below were collected, and we were provided with uniform information from every case, which served as a basis of comparison later in judging results. The thirty days' bed-rest was deemed important because this eliminated the variable effects of unsupervised muscular exertion which might have clouded subsequent observations. For the same reason and because more safety could be promised the patients by such care, bed-re. . was continued throughout the treatment. . . . A sufficient number of nurses was on duty so as to ensure a continuous ward routine. [Here I omit the clinical and laboratory examinations and the frequency with which they were made.]

"The patients treated as controls each received distilled water [in the same manner as the treated group received the drug].

"LABORATORY FINDINGS

[I shall omit the six pages on this subject but do want to quote a footnote:] "Details of . . . [the blood chemistry] were carried out by one man [who] had no other routine duties. All X-ray interpretations were made independently by another man. . . . The films were read by key number so that the interpretation would not be influenced by a knowledge of the clinical course of the case. . . . All laboratory specimens . . . were [also] labelled [only] with a key number.

"Effects on the Tuberculosis:

[The author then packs several pages with a detailed examination of the data in the two groups of patients (Control vs. Treated) on temperature, pulse, fatigue, body weight, sputum weight, cough, appetite, sleep, pain in the chest, hemoptysis, dyspnea, and physical findings, which I must omit for the sake of brevity. For the same reason I omit two pages on "Toxic Effects Referable to the Drug"]

"Local Pulmonary Manifestations:

"X-ray Findings: Experience has shown that serial roentgenograms, made according to a uniform technique, are the best means of detecting anatomical changes in pulmonary tuberculous lesions. In this study, therefore, great reliance was placed on the X-ray films to show the actual state of the lungs from time to time. . . . In the control group the X-ray showed in general a slight, though definite healing trend. In the treated group the greater tendency to unfavorable progression of the disease is clearly shown in 5 cases. In 6 cases improvement was noted, but this was striking in only one. . . . Healing changes consisted mainly of absorption of exudative deposits and the diminution of cavities. . . .

"Sputum: In the literature, one of the outstanding claims for [the drug] is its alleged power to reduce the bacillary content of the sputum. We were unable to detect this influence in our treated patients.

"DISCUSSION

"Possible Modes of Action: Question of Specific Effect:

"In human pulmonary cases, evidence of considerable weight in relation to this allegedly specific effect should be obtained from a study of changes in the bacillary content of the sputum. Many clinicians have stressed this feature, and a recent paper reports, for example, that 29 of 78 treated patients lost tubercle bacilli from their sputum, while a like change occurred in only 7 of 65 'control' cases. Many of the treated cases [in this series] lost their bacilli after [a short course] of the drug. This would seem to argue strongly for a sterilizing effect, but a close examination of the methods [which were employed] reveals certain defects which seriously impair the value of [such] inferences. In our own study, we considered the sputum examination as a factor of great importance and set up the criterion that at least

two ample specimens must give negative results in microscopical examination (after digestion and concentration), culture and guinea-pig inoculation before the sputum could be called negative. By applying this criterion we found no evidence whatever that the drug has a sterilizing effect on the living human tuberculous organism.

[In commenting upon the symptoms appearing during treatment, our medalist remarked]: "A tuberculin-like effect may be an actuality but since there is very slender evidence that this could be due to the killing and distintegration of tubercle bacilli lodged in existing lesions, a more reasonable explanation must be sought.

"A certain group of induced symptoms . . . could be interpreted, at least to some extent, as the constitutional effects of circulating tuberculosis 'toxins' which may be liberated from existing tuberculous lesions by some action of the drug. However, a nonspecific action, resulting in an alteration of capillary premeability about the tuberculous lesions, would seem to be wholly sufficient to produce such effects. We do not believe it is necessary to assume a specific bacteriotropic action, —especially since, at the present time, this would be pure assumption. [We believe the symptoms are manifestations of toxicity caused by the drug.] This explanation is simple and logical, relieving one of the necessity of constructing a highly improbable hypothesis of a special kind of tuberculous intoxication induced by [the drug].

"Criteria for Judging the Clinical Effects of a Chemotherapeutic Agent:

"The clinical testing of any therapeutic agent for human tuberculosis and the formulation of a judgment of the results, give pause to the physician who has dealt at length with the disease. A recollection of the multitude of remedies, often vaunted by very conscientious men, that have had their little day and then passed into obscurity, sometimes sorely tries one's faith in the value of clinical observation. First of all is the notorious tendency of the disease to fluctuate naturally through all the phases of progression and retrogression, sometimes because of treatment; sometimes for the lack of it; often despite it. It requires the utmost watchfulness to avoid the mistake of ascribing causal relationships to events which are merely coincidental, since tuberculosis is more deceptive in this respect than are many other diseases. The difficulty is multiplied if one relies solely for his judgment on the use of a therapeutic agent as a part of the routine procedure in an institution. A carefully prearranged plan of study, ordinarily including some unusual tests and examinations, is quite necessary to discover the more subtle effects of such an agent with any degree of precision. With this condition satisfied, a clinical trial often will yield knowledge which cannot be obtained entirely from laboratory experimentation. Tuberculosis in animals never duplicates exactly all the features of the disease in man, and, therefore, there is not only a place but a real necessity for clinical testing.

"To us, many clinical reports on the use of this drug seem misleading and valueless because the manner of observation of patients under study has not been sufficiently careful and exacting. In many instances, the drug was introduced as an addition to ordinary institutional treatment and results have been judged on vague and insufficient evidence. Very few workers have divided their cases so as to have closely comparable 'control' groups. Some of those who have attempted to select such controls have used the extent of the disease as the basis of selection. Knowing, as we do, that in many cases the character of the lesion means vastly more than its extent, the matching of cases solely according to their position in [any] classification [scheme] cannot be accepted as a proper step in work of this purpose. Others have eliminated from comparison those cases in which the drug was tried but found not to be well tolerated, a self-condemnatory practice.

"The main argument in the reports of some writers [on this drug] is the change in the bacillary content of the sputum during treatment. Few, however, describe

their sputum-examination technique, and many if not most of them rely on the microscopical examination of single sputum smears. In our experience, this method is very inaccurate for purposes of such a study. Concentration and digestion of the sputum before staining yields 15 to 20 per cent more positive; culture and animal inoculation still more. Since our cases received about the same amount of drug as most cases reported in the literature, the absolute contradiction between our sputum findings and those of some others is significant even though our group of patients is not large. We believe this is to be explained partly, if not largely, on the fact that our method of searching for the bacilli was much more thorough and accurate. No investigation of this type can be considered adequate if it does not incorporate such exhaustive methods.

"We report, finally, on only 12 treated cases and 11 'controls.' Ordinarily this small number would be insufficient to afford much information. However, what the investigation loses by lack of extensiveness, we believe, is made up by its intensiveness and by the thoroughness of the method pursued."

For the medalist's conclusions and for a fuller understanding of the implications of the work from which I have just read, I refer you to pages 401–435 of the October issue of the AMERICAN REVIEW OF TUBERCULOSIS for the year 1931. The work was begun in 1926, and the follow-ups were made in 1928 and 1930. The drug was a gold salt, sanocrysin. Your committee belatedly but proudly awards the Trudeau Medal to the senior author, the widely beloved physician and teacher, the "good student who was forever becoming one more completely," Dr. James Burns Amberson, Jr.

DR. POPE: At the time our Selections Committee made its choice, it had no way of knowing that Dr. Amberson had already made commitments which made it absolutely impossible for him to be with us tonight. In fact, at the time we are meeting here this evening, Dr. Amberson is meeting with the Association of British and Irish Physicians in Sheffield, England. He went abroad on the seventh of May to fulfill the commitment which he had made previously to the staff of the Brockton Hospital, London, for a series of department lectures there and for a meeting of the British Tuberculosis Association. It is, I am sure you will agree, characteristic of the man that, when faced with this difficult choice, Dr. Amberson with little hesitation decided that his obligations were with the people and with the organizations to which he had previously made commitment. Dr. Amberson, on notification of the award, in order that he might be present tonight, sent us this letter.

LETTER FROM DR. AMBERSON ACKNOWLEDGING NOTIFICATION OF TRUDEAU MEDAL AWARD FOR 1952

Gentlemen:

The notification that I have been designated to receive the 1952 award of the Trudeau Medal stirs such deep feeling that I am unable to compose an adequate expression. The award must have different meanings to many people. To me it has the greatest of meaning because I take it as a token of friendship of the members of this Association with whom I have met, conferred, and worked during thirty odd years. As a beginner in the activities of the Association in 1918, I found the cordiality and interest of the older members to be most kind and stimulating. Through the following years, I had the good fortune of finding numerous friends here—friends who have been interesting, loyal, and helpful. It is this which, above all else, makes me so grateful to the Association.

To have participated for so many years in your work has been a privilege of

highest value to me. Certainly, one can have a just and lasting pride in its accomplishments.

I regret that circumstances prevent my being present in Boston to receive the award—one of the brightest moments of my life. My heart and spirit will be there bearing my gratitude to all my friends for this great honor.

DR. POPE: As Dr. Amberson was spared the reading of this citation, he could not know the part of his work which has just been quoted. Knowing him as we all do, I am sure he would want me to give credit to his associates in this work that he did in his article. Among them were: Henry Vaughn, then Commissioner of Health of Detroit, now Dean of the School of Public Health, University of Michigan, and honorary member of the Trudeau Society; Bruce H. Douglas, then Medical Director of Maybury Sanatorium and later president of the American Sanatorium Association and one of the founders of the movement which resulted in the evolution of the American Sanatorium Association into the American Trudeau Society. Those of you who are of the generation of Dr. David Lyman and myself will remember that it was in this hall at the annual meeting in 1939 when the association was last in Boston that this memorable change in the organization of the American Sanatorium Association took place. In addition to Dr. Douglas and Dr. Vaughn, another of his associates was Dr. Max Pinner, then head of the Trudeau Laboratory and later editor of THE AMERICAN REVIEW OF TUBERCULOSIS and himself a Trudeau Medalist in 1946. One of the distinguishing characteristics of Dr. Amberson was that he always found himself in association with competent and disinterested workers.

NOTES

ANNUAL MEETING OF THE AMERICAN TRUDEAU SOCIETY—1953

The American Trudeau Society, medical section of the National Tuberculosis Association invites the submission of abstracts of scientific papers for presentation at its next annual meeting in Los Angeles, California, May 18 to 22, 1953, at the Hotel Biltmore.

Full information can be obtained by writing to the Chairman of the Medical Sessions Committee, American Trudeau Society, 1790 Broadway, New York 19, N. Y.

SEMINAR ON PULMONARY FUNCTION

The University of California School of Medicine, University Extension in cooperation with the American Trudeau Society and the Medical Faculty of Stanford University, will conduct a seminar on Pulmonary Function, February 6, 7, and 8, 1953, at Toland Hall, University of California Hospital, San Francisco. The fee for the course is $50.00 and the course is open only to graduates of medical schools approved by the council on Medical Education and Hospitals of the American Medical Association. Those who wish to register should write to Stacy R. Mettier, M.D., Head of Postgraduate Instruction, Medical Extension, University of California Medical Center, San Francisco 22, California, giving year of graduation, medical school, and enclosing a check or money order for $50.00, payable to The Regents of the University of California.

POSTGRADUATE COURSE ON "THE MEASUREMENT OF PULMONARY FUNCTION"

The American Trudeau Society and the Medical Schools of Harvard University, Tufts College, and Boston University are co-sponsors of a post-graduate course "The Measurement of Pulmonary Function in Health and Disease" to be held in Boston, March 9–13, 1953. This is a beginner's course aimed at physicians interested in diseases of the chest, who wish to acquaint themselves with the ABC's of methods used in the evaluation of pulmonary function. Demonstrations with patients will be featured. The tuition will be $50.00. Applications and information may be obtained from Edward J. Welch, M.D., Chairman, 1101 Beacon Street, Brookline 46, Massachusetts.

PRIZE FOR PAPER ON DIABETES BY MEDICAL STUDENTS AND INTERNS

The American Diabetes Association offers a $250.00 prize to *medical students* and *interns* for a paper on any subject relating to diabetes. The paper can be a report of original studies, a biographical or historical note, a case report with suitable comment, or a review of the literature.

This incentive is particularly apropos in the field of diabetes since Dr. Paul Langerhans made his studies of the pancreas, describing the islets that bear his name, while he was an undergraduate student in Berlin in 1869; and Dr. Charles H. Best, while a graduate student, was co-discoverer of insulin in 1922.

Manuscripts must be submitted on or before April 1, 1953, to the Editorial Offices of *Diabetes:* The Journal of the American Diabetes Association, 11 West 42nd Street, New York 36, New York. The papers will be reviewed by the Editorial Board, which will take into consideration the value of the material and method of presentation in selecting the best paper.

The award of $250.00 has been made possible through the generosity of the St. Louis Diabetes Association, an affiliate of the American Diabetes Association.

V. MEXICAN NATIONAL CONGRESS OF TUBERCULOSIS AND SILICOSIS

The V. Mexican National Congress of Tuberculosis and Silicosis will take place in Guadalajara, Jalisco, Mexico, January 25 to 31, 1952.

It will be held at the School of Medicine of the University of Guadalajara, under the auspices of this University and the government of the State of Jalisco. It is organized by the Sociedad Mexicana de Estudios Sobre Tuberculosis y Enfermedades del Aparto Respiratorio.

FORMATION OF THE QUEBEC CHAPTER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

At the joint meeting of La Société de Phtisiologie de Montréal et de Québec and the Section Tuberculosis of the Montreal Medico-Chirurgical Society held at the Sacred Heart Hospital, Cartierville, the President of the American College of Chest Physicians, Dr. Andrew L. Banyai, and the Executive Director, Mr. Murray Kornfeld, officially inaugurated the Quebec Chapter of the A.C.C.P., the first of its kind in Canada.

The following were elected on the executive, all Fellows of the A.C.C.P., Member ex-officio:

"Dr. B.-G. Bégin, Governor of the A.C.C.P. for the Province of Quebec."

President: Dr. Fernand Hébert, Medical Director at the Sacred Heart Hospital

1st Vice-President: Dr. G. R. Howell, Medical Director at the Grace Dart Home Hospital

2nd Vice-President: Dr. G. Grégoire, Director of the Antituberculosis Clinic, Quebec City

Treasurer: Dr. A. Hickey, Assistant Medical Director at the Royal Edward Laurentian Hospital, Ste-Agathe

Secretary: Dr. J.-J. Laurier, Assistant Medical Director at the Sacred Heart Hospital, Cartierville.

NECROLOGY

Dr. Ananta Roy Chowdhury, New Delhi, India
Dr. Louis Cohen, Philadelphia, Pennsylvania
Dr. Seth L. Cox, Seattle, Washington
Dr. Gustave Derscheid, Brussels, Belgium
Dr. G. Burton Gilbert, Colorado Springs, Colorado
Dr. Clarence F. Graham, Ithaca, New York
Dr. Kurt Joachim Jessner, Fairfield, Maine
Dr. Paulo Leiria, Rio Grande do Sul, Brazil
Dr. Albert H. Garvin, Buffalo, New York
Dr. Charles M. Oberschmidt, Memphis, Tennessee
Dr. Friedrich Wilhelm Pitsch, Freiburg/Breisgau, Germany
Dr. Dick H. Saley, Northville, Michigan
Dr. Jacob J. Wiener, New York, New York

THE AMERICAN REVIEW OF TUBERCULOSIS ABSTRACTS

Edited by LAWRENCE B. HOBSON

VOLUME 67 JANUARY, 1953 ABST. No. 1

CLINICAL STUDIES, TUBERCULOSIS

Miliary Tuberculosis During Cortisone Therapy.—A patient with lupus erythematosis was treated with cortisone. Radiograms over a four-year period up to the time of institution of therapy showed no evidence of tuberculosis. Nevertheless, she developed miliary tuberculosis. It is likely that the disease spread from a latent focus.—*Disseminated lupus erythematosis complicated by miliary tuberculosis during cortisone therapy, J. N. Harris-Jones & N. K. Pein, Lancet, July 19, 1952, 2: 115.—(A. G. Cohen)*

Miliary Tuberculosis of the Liver.—A 29-year-old female was hospitalized with temperature up to 103°F. and considerable liver enlargement. The history and examination were unrevealing. A liver biopsy disclosed numerous periportal tubercles, some of which showed beginning caseation. During an eight-month course of streptomycin, the patient progressively defervesced, the liver became smaller, and the patient gained weight. Four successive biopsies showed scarring of most of the tubercles, starting in the third month, so that after eight months the liver had become histologically normal and treatment was discontinued. The patient remained well during the year up to the time of writing. A second case of isolated miliary tuberculosis of the liver occurred in a 28-year-old woman whose fever of 103°F. started immediately before delivery and continued one week thereafter. She had hepatomegaly but chest roentgenograms and blood cultures were negative. On biopsy, the liver was found to be studded with partly caseous tubercles. Tubercle bacilli were found in the stools but not in the gastric juice. A seven-month course of streptomycin caused her fever and hepatic enlargement to disappear and she gained weight. Four liver biopsies showed scarring of the tubercles. The origin of the liver tuberculosis from a latent mesenteric tuberculosis is considered probable in these 2 cases.—*La tuberculose miliaire du foie (granulie hépatique portogène d'allure primitive), M. Janbon & L. Bertrand, Presse méd., December 8, 1951, 59: 1631.—(V. Leites)*

Tuberculosis in Patients with Leprosy.—Among 119 cases of tuberculosis seen at the Curupaití Leprosy Asylum in Brazil during the three-year period July, 1948, to July, 1951, 27 deaths from tuberculosis occurred. The tuberculosis death rate has risen from 14.0 per cent of the total death rate in 1948 to 24.1 per cent in 1951, possibly because of improved diagnosis. Tuberculosis morbidity rates in leprosy patients roughly parallel those for the general population in Rio de Janeiro. Use of new drugs and methods has improved considerably care of these patients in the last few years. Among 119 cases of tuberculosis detected in 1948 to 1951, 101 were in lepromatous type cases and only 18 among tuberculoid cases. Minimal and moderate lesions have of late become more common. It is estimated that there are 5,000 to 6,000 lepers at large in the Federal District in Brazil, and it is likely that 600 to 700 of them also suffer from tuberculosis. These cases should be located and given proper treatment.—*Tratamento da tuberculose em Hanseninaos. Mortalidade por tuberculose em Curupaití. Mortalidade, morbidade e profilaxia da tuberculose em doentes de lepra, S. de Oliveira Lima, Rev. brasil. tuberc., March-April, 1952, 20: 105.—(A. A. Moll)*

Transplacental Tuberculous Infection.—Fatal congenital tuberculosis was observed in 2 infants. The first was asphyctic at birth and revived only after half an hour of artificial respiration. Lumbar puncture revealed intracranial hemorrhage, and the infant died forty-eight hours after birth. At autopsy there were found: bilateral rupture of the tentorium cerebelli, intratentorial hemorrhage, and massive acute catarrhal bronchopneumonia, as well as miliary tuberculosis of the liver, spleen, meninges, and tonsils. The diagnosis of tuberculosis was confirmed histologically. Infection by way of the placenta seems certain. The second child was born prematurely of a mother who died shortly after delivery as a result of miliary tuberculosis and basalar meningitis confirmed by autopsy. The infant had no contact with the mother or any other tuberculous person. Despite special care, the child lost weight and died when sixty-one days old. The autopsy showed generalized tuberculosis of the lung, pleura, spleen, kidneys, and lymph nodes. Histologically, tuberculosis was present and it probably was acquired from the mother by way of the placenta.—*Transplacental tuberculous infection of newborns* (*Yugoslav*), *S. A. Kostic-Jostic, Tuberkuloza, December, 1951, 3: 351.*—(*J. Ilavsky*)

Cutaneous Primary Complex.—Primary tuberculous complex of the skin is not rare in Yugoslavia. Tubercle bacilli can be inoculated by trauma, through nontuberculous lesions, or without visible cutaneous damage. The incubation period varies from eight days to four months. The primary lesion is a small, dark red papule or a small ulcer which may be complicated by another bacterial infection. The skin lesion heals promptly but adenopathy of the regional lymph nodes, which appears next, is much more persistent. The prognosis is good and streptomycin therapy is very effective, as shown by the satisfactory results in 4 children. The first child, a newborn, was infected by a kiss on the nose, where the primary ulcer appeared. Bilateral, fluctuant, cervical lymphadenitis developed soon thereafter. A two-year-old girl had angular conjunctivitis and periauricular lymphadenitis, tubercle bacilli being cultured from the glands. The third child, a two-year-old boy with a fluctuant right inguinal lymph node, had a healed scar on his toe suggestive of an earlier primary ulcer there. The remaining patient was a seven-year-old girl who developed tuberculous left inguinal adenitis after a wound on the left knee.—*Tuberculous primary complex of the skin* (*Yugoslav*), *K. Parsini, B. Puretic, & I. Svel, Tuberculoza, December, 1951, 3: 411.*—(*J. Ilavsky*)

Transient Lesions in Hilar Tuberculosis.—Two children of tuberculous parents had strongly positive tuberculin reactions and old, healed, hilar tuberculous foci. The first child had an attack of follicular tonsillitis, after which a roentgenogram showed a large perihilar density with an indistinct peripheral margin. Ten days later this density had disappeared but an old, healed, perihilar focus was visible. The second child had a similar density, found thirty to thirty-five days after smallpox and diphtheria immunization. Ten to twelve days later this shadow also had disappeared. The short duration of the process in these cases shows that they were not tuberculous. They may have been "paraallergic" reactions provoked about old tuberculous foci by nonspecific allergens.—*Para-allergic manifestations of hilar tuberculosis* (*Yugoslav*), *T. Drinkovic, Tuberkuloza, December, 1951, 3: 407.*—(*J. Ilavsky*)

Hilar Adenopathy and Typhoid.—Under the conditions prevalent in Yugoslavia, tuberculosis must be considered in the differential diagnosis of typhoid or "enteric" fever. Tuberculous tracheobronchial adenopathy frequently causes prolonged fever with a positive Widal reaction. Anti-typhoid agglutinins often appear in the blood during infectious diseases such as tuberculosis, or even after BCG vaccinations. Of 12 patients tested, 5 yielded a titer greater than 1:200, usually attributable to an anamnestic Widal reaction. The relative well-being, the roent-

genographic changes, and the relatively slight immunologic changes can distinguish the cases of hilar adenopathy from those of typhoid fever.—*Adenitis of the pulmonary hilum and typhoid (Yugoslav), R. T. Brezjanin, Tuberkuloza, December, 1951, 3: 406.—(J. Ilavsky)*

Coexisting Coccidioidomycosis and Tuberculosis.—Coccidioidomycosis and tuberculosis occurred together in 2 Mexican children and one Negro child in an endemic area of coccidioidomycosis in California. In each case, tuberculosis was proved bacteriologically and coccidioidomycosis by positive complement-fixation tests. One child who had primary pulmonary tuberculosis and primary pulmonary coccidioidomycosis responded well to streptomycin and *p*-aminosalicylic acid. In another case of coccidioidomycosis and primary pulmonary tuberculosis, *C. immitis* spherules were recovered from an abscess on the forehead and the mycelial form was cultured. The skull also contained two coccidioidal granulomas. Despite streptomycin for the tuberculosis and stilbamidine for the disseminated coccidioidomycosis, the child died and the clinical findings were substantiated by post-mortem examination. Death was attributed to toxic effects from stilbamidine although these effects have not been reported. The remaining child had tuberculous cervical adenitis, together with primary pulmonary coccidioidomycosis and responded well to bed rest.—*Coexisting coccidioidomycosis and tuberculosis in children, R. Cohen, J. Bos, & P. A. Webb, Arch. Pediat., June, 1952, 69: 267.—(M. J. Small)*

Protracted Asthenia.—The "syndrome of tuberculous impregnation" is a chronic state of continuous or intermittent slight fever and asthenia, associated with various functional disturbances which lasts for years in the absence of a demonstrable active tuberculous lesion. Of a total of 137 patients, often followed for decades because of chronic debility and slight fever, one-third developed pulmonary or extrapulmonary tuberculous episodes while under observation. Almost all of the patients gave a family history of tuberculosis. Approximately 80 per cent had had a tuberculous incident indicated by primary or postprimary tuberculosis, pleurisy, or extrapulmonary tuberculosis in the past or by fibrotic or calcific sequelae on the roentgenogram. During the entire observation period of thirty years, there were 8 deaths from tuberculosis in this group. It is believed that all prolonged states of slight fever and "constitutional" asthenia accompanied by some indication of previous tuberculous infection, even if abortive or healed, should point toward the diagnosis of "tuberculo-toxic impregnation." The results with tuberculin therapy are good.—*Le pronostic et l'évolution des syndromes d'imprégnation tuberculeuse d'après une enquête portant sur 137 cas, R. Burnand, Rev. de la tuberc., 1952, 16: 312.—(V. Leites)*

Bullous Tuberculosis.—Five cases of bullous tuberculosis were observed from 1949 to 1951 among children hospitalized for extensive primary tuberculosis. Four of the children had miliary tuberculosis; the fifth had large isolated mediastinal, pulmonary, and cerebral lesions. All of the 4 patients from three and one-half to twenty-two months old died; the fifth child was four years old and survived the acute respiratory episode. All of the children suddenly became dyspneic during the course of severe primary tuberculosis. One child developed fatal spontaneous pneumothorax; another had extensive mediastinal and subcutaneous emphysema. Roentgenograms following these acute symptoms showed widespread bullous changes in the lungs as well as the earlier pathology. Autopsies showed extensive bullous emphysema throughout both lungs in 3 cases and bullous emphysema confined to the left upper lobe in one case. The bullae varied in size and were distributed throughout the entire parenchyma. Caseous lymph nodes had ruptured into a bronchus in 2 cases; in the other cases, the lungs were not examined so thoroughly. Microscopically, the walls of the numerous bullae were lined with

necrotic caseous tissue. These changes arose when the rupture of caseous nodes into the bronchial tree established a check-valve mechanism disturbing the ventilation so that acute bullous dilatation occurred.—*La tuberculose bulleuse de l'enfant, R. Debré, R. Grumbach, & L. Pichon, Semaine d. hôp. Paris, July, 1951, 27: 2207.*—(*V. Leites*)

Genital Tuberculosis.—Surgical intervention, as well as streptomycin, was employed in 27 cases of genital tuberculosis in women. Streptomycin was given at least eight weeks preoperatively and at least three weeks postoperatively. The following procedures were done: total hysterectomy and bilateral salpingo-oophorectomy in 16; total hysterectomy and unilateral salpingo-oophorectomy in 2; total hysterectomy, bilateral salpingectomy, and unilateral oophorectomy in 3; and subtotal hysterectomy and bilateral salpingo-oophorectomy in 3 patients. There were 2 deaths. The complications were accidental cystotomy in one, fecal fistula in 2, carcinoma of the cervix in one, and wound infections in 3 patients. The finding of a "doughy abdomen" has been common during the follow-up period of two and one-half years. There was no beneficial influence on associated pulmonary lesions.—*Streptomycin in genital tuberculosis of female; further observations, H. Sered, F. H. Falls, & B. P. Zummo, J. A. M. A., February 16, 1952, 148: 521.*—(*H. Abeles*)

Pelvic Tuberculosis in the Female.—Until thirty years ago, pelvic tuberculosis was considered rare. Now it is known that 5 to 7 per cent of all pelvic infections that require operations are tuberculous. In women the reproductive organs rank fourth in frequency of tuberculosis after the lungs, intestinal tract, and peritoneum. Tuberculosis of the female genitalia, exclusive of tuberculous peritonitis, is assumed to be hematogenous in origin, and the primary focus is found elsewhere, usually in the lungs or kidneys. Primary ascending infection is rare. Pelvic tuberculosis attacks the Fallopian tubes in almost every case, the endometrium in three-fourths, and the ovaries in one-third of the cases. It almost never attacks the urethra, vagina, or cervix, in contradistinction to gonorrhea. Tuberculous peritonitis is a common complication of pelvic tuberculosis; chronic peritoneal tuberculosis, for all practical purposes, is always secondary to tuberculosis of the Fallopian tubes, tuberculous mesenteric lymph nodes, or ulceration of the bowel. The diagnosis of pelvic tuberculosis is difficult. The patients, usually between fifteen and thirty-five years of age, complain of either amenorrhea or more often menorrhagia, weight loss, night sweats, and evening fever. About ten years ago, conservative therapy was recommended although some gynecologists preferred hysterectomy and bilateral salpingo-oophorectomy plus roentgenotherapy. Streptomycin has been used in doses as large as 1 to 2 gm. daily for approximately four months. Since 1948, 9 patients with pelvic tuberculosis have received streptomycin as a supplement to surgery, the drug being given in various doses averaging 2 gm. daily for two months. One patient died and the other 8 improved.—*Pelvic tuberculosis in the female, J. M. Cox & I. B. Higgins, J. Nat. M. A., July, 1952, 44: 278.*—(*B. Hyde*)

Arteriobronchial Fistula in Tuberculosis.—In 2 cases of pulmonary tuberculosis, with apparently stabilized lesions, the course was marked by sudden, profuse hemoptyses. The blood was non-frothy and the bleeding stopped as abruptly as it began. In each case operation disclosed an arteriobronchial fistula involving either a main trunk or a lobar branch. In each case the presence of a thrombus within the artery explained the intermittency of the bleeding. Resection was carried out in each case. The operative procedures were made difficult by the presence of matted hilar nodes. These were probably tuberculous in origin and were most likely the cause of the fistulas.—*Massive haemoptysis from arterio-bronchial fistula in pulmonary tuberculosis, M. Berard and J. de Beaujeu, Thorax, June, 1952, 7: 152.*—(*A. G. Cohen*)

Artificial Pneumothorax.—Artificial pneumothorax was induced by deliberate lung puncture. A needle attached to a 21 cc. syringe was inserted into the lung until air bubbles could be aspirated. The needle was then withdrawn. This was the entire procedure. Induction was attempted in 78 cases, with success in 71 and failure after at least 2 attempts in the other 7. In 3 of the failures, further attempts by the traditional method were unsuccessful. In most of the cases, a shallow pneumothorax was obtained. In 2 cases, excess collapse necessitated aspiration of air. The timing of the first refill ranged from the first to the fourth day. No complications ensued.—*Induction of artificial pneumothorax by lung puncture, E. N. Moyes & J. K. Scott, Lancet, June 28, 1952, 1: 1278.*—(*A. G. Cohen*)

Exudate in Pneumoperitoneum.—Roentgenography of the small pelvis in the lateral recumbent position after an abundant refill demonstrated small quantities of fluid in 18 of 25 patients with penumoperitoneum. The pneumoperitoneum had been induced several days, weeks, or months previously; 7 of 9 patients developed exudate within the first few weeks. There was no correlation between the nature or extent of pulmonary lesions and the occurrence of intra-abdominal fluid. The exudates were serofibrinous and did not contain tubercle bacilli. The only consequences were peritoneal thickening, allowing smaller refills, and occasional adhesions.—*L'épanchement abdominal latent du pneumo-peritoine therapeutique, G. Roche & M. Odabachian, Rev. de la tuberc., 1952, 16: 388.*—(*V. Leites*)

Pulmonary Resection in Tuberculosis.—In a series of 325 consecutive pulmonary resections for tuberculosis the usual indications were thoracoplasty failure, bronchiectasis, bronchostenosis, lower lobe lesion, pneumothorax failure, destroyed lung, mistaken diagnosis, nodular lesions, and upper lobe cavity. Of the 325 patients, 264 achieved an inactive status lasting one to seven years, 29 remained positive, 28 died, and 4 could not be traced. The most serious complication was bronchopleural fistula, which occurred in 5 of the 18 cases considered as operative deaths; 10 of the deaths were considered nonoperative. Other complications included tuberculous pneumonitis which was contralateral and fatal in 5 cases, and pulmonary insufficiency which was encountered 3 times. This series does not include patients treated by the present preparatory routine of long uninterrupted courses of daily *p*-aminosalicylic acid and biweekly streptomycin. This therapy should be used, however, to obtain maximal resolution of disease and preservation of pulmonary tissue. With such a program, bilateral surgery need not be hazardous. Pathologic studies of the resected specimens confirmed the presence of tubercle bacilli, and it is concluded that surgical intervention to remove major residual foci offers the greatest protection against recurrence.—*Pulmonary resection in tuberculosis, J. W. Gale, H. A. Dickie, & A. R. Curreri, Ann. Surg., July, 1952, 136: 132.*—(*M. J. Small*)

Lower Lobectomy for Tuberculosis.—Among 58 consecutive cases of lower lobe lobectomy for tuberculosis, there were 37 men and 21 women, ranging in age from four to forty-six years, with an average of twenty-seven years. In 13 instances, the middle lobe as well had to be removed. The most serious technical difficulties were (*1*) a large cavity in the apex of the lower lobe which overrode the fissure to involve the adjacent lobe and (*2*) infection of the lymph nodes which had become so intimately involved with the artery as to make separation almost impossible without tearing the vessel. Indications for the operation were tuberculoma in 8 cases, bronchial stenosis in 18, and tuberculous cavity in 41. Of 37 patients followed for more than one year postoperatively, 12 have been observed more than three years. To date, there have been 4 deaths (6.8 per cent). One of these patients had a contralateral fibrothorax and died in respiratory failure; the other 3 had large cavities which overrode the fissure. All had received large doses of

streptomycin prior to operation and their organisms were presumably resistant. Four patients (6.8 per cent) developed homo- or contralateral disease and are still under treatment. There were 4 (6.8 per cent) with empyema who are still under treatment. The remaining 48 (79.6 per cent) are well, most of them having returned to their former occupations.—*Notre expérience de la lobectomie inférieure pour tuberculose, Bérard, P. Juttin, & L. Grézard, Poumon, April, 1952, 8: 369.—(F. S. Lansdown)*

Apicolysis.—Of 65 patients treated with thoracoplasty and extrafascial apicolysis, 52 (80 per cent) had good results by tomographic and bacteriologic criteria. There were 5 reactivations, 2 patients with residual cavity, and 2 patients with sputum positive for tubercle bacilli without evidence of cavitation. Three patients developed infection of the apicolysis pocket. Of 36 patients with cavities measuring more than 5 cm. in diameter, 26 showed cavity closure; of 23 patients with medium-sized cavities, 22 had good results. There was one postoperative death due to auricular thrombosis. There was operative injury to the lung in 3 cases and injury to the veins in 2 cases. There were six cases of postoperative neuritis and 2 cases of brachial paralysis. Two patients developed postoperative atelectasis; 3 had postoperative phlebitis. The advantages of extrafascial apicolysis are such that it should always be performed if, at the end of a thoracoplasty, the apex remains attached to the vertebral column. In giant cavities of the upper lobe, thoracoplasty was usually started from below and completed by extrafascial pneumonolysis, a procedure which reduces the risk of residual cavitation.—*La place actuelle de l'apicolyse extrafasciale dans le traitement chirurgical de la tuberculose pulmonaire, Pierre-Bourgeois, M. Iselin, G. Thomeret, & G. Rollin, Semaine d. hôp. Paris, April, 1952, 28: 1344.—(V. Leites)*

Plombage Apicolysis.—Apicolysis with plombage was performed in 50 patients with pulmonary tuberculosis, including 27 women and 23 men. In 4 of them, the process was bilateral. In 45, the sputum became negative and favorable clinical results were manifested by general improvement, subsidence of symptoms, and the absence of roentgenographic findings. A few patients have been discharged but most of them remain in the sanatorium. In 5 cases with persistently positive sputum, the plombage filling was removed and pneumothorax was substituted. As the procedure is relatively benign, it may be tried either alone or with other collapse measures, even in weak patients. The ping-pong balls used for plombage were perfectly tolerated. The best indications for this treatment are small apical cavities with limited fibrotic changes and all apical lesions.—*Apicolisis con plombaje, S. Huaco Vizcardo, Rev. tuberc., January–December, 1951, 11: 92.—(A. A. Moll)*

Pleural Prosthesis After Pneumonectomy.—In 3 instances acrylic balls were used to fill the dead space following pneumonectomy for tuberculosis. If a space remains after such an operation there may be persistence or reaccumulation of fluid which often contains tubercle bacilli, bronchopleural fistula, deviation of the mediastinum, and increased risk of breakdown in the contralateral lung. Thoracoplasty is unsatisfactory because it involves a second operation, it reduces but does not abolish the dead space, and it causes a marked scoliosis. The first case was of a young woman who developed bronchopleural fistula after pneumonectomy. An extramusculo-periosteal pneumothorax was induced and the pocket was filled with acrylic balls. Six months after the operation the result appears excellent. In the other 2 cases the balls were placed in the pleural cavity immediately following pneumonectomy, thus being covered with pleura or neo-pleura. These patients are in good condition two and three months, respectively, after operation. There is evidence of a little liquid in the interstices, presumably undergoing organization.—*Traitement de la cavité libre après pneumonectomie, Métras & Grégoire, Poumon, April, 1952, 8: 313.—(F. S. Lansdown)*

Treatment of Tuberculous Cavities.—Of the methods of "open treatment" of tuberculous cavities, cavernostomy seems the best. Results were good in 5 cases of residual cavity after thoracoplasty or of cavities located in the lower parts of the lung and unsuitable for resection. Monaldi's endocavitary aspiration should be used only for large or tension cavities. Although the use of antibiotics may improve the results, 55 cases treated by aspiration did not give uniformly good results. Maurer's "speleostomy" was not employed by the author.—*Open treatment of tuberculous pulmonary cavities* (*Yugoslav*), *S. Krstic, Tuberkuloza, December, 1951, 3: 336.*—(*J. Ilavsky*)

Pneumonolysis and Thoracoplasty.—New drugs have not removed the need for the surgical treatment of cavitary tuberculosis but have decreased the operative risk. Of 131 patients upon whom pneumonolysis was performed in Belgrade, 7 had pleural section and 6 had intra- and extra-fascial pneumothorax. In 2 cases, a second pneumonolysis was performed because of persistent cavities and, in 13, hematomas later had to be removed. Despite liberal indications for operation and bilateral disease in one-fourth of the cases, 104 patients no longer expectorated tubercle bacilli. There were only 6 serious complications; 3 patients had thoracic fistulas, 2 had pulmonary fistulas, and one died immediately after operation. Of 77 patients who had thoracoplasty, 9 had one-stage operations; the remainder had two stages. The thoracoplasty was later corrected in 2 cases. Subtotal thoracoplasty was most common although a partial upper rib resection was sometimes used. Somber's operation with apicolysis was rarely performed. Among the 77 patients, cavities disappeared in 78 per cent and the sputum became negative in 75 per cent. The incidence of early death was 3.8 per cent and that of pulmonary fistulas, 1.3 per cent.—*Thoracoplasty and pneumonolysis performed at the Department of Phthisiology in Beograd during the past two years* (*Yugoslav*), *M. Grujic & M. Budislavjevic, Tuberkuloza, December, 1951, 3: 363.*—(*J. Ilavsky*)

Streptokinase and Streptodornase.—In 9 cases of extrapleural pneumothorax, streptokinase and streptodornase were used to obtain lysis of blood clots and fibrin membranes in the extrapleural space. Relatively small doses were employed, the largest being 100,000 units of streptokinase and 25,000 units of streptodornase. In the other cases, 25,000 to 75,000 units of streptokinase and 6,000 to 20,000 units of streptodornase were given. In 4 of the 9 cases, the local results were satisfactory and the general reactions lasted only a few days; two or three aspirations were sufficient to obtain a dry extrapleural space. In the remaining 5 cases, however, the general reactions were severe with rapid weight loss of 5 or 6 kg., profound asthenia, anorexia, and fever as high as 103° or 104°F. with slow defervescence. The fluid recurred in spite of frequent aspirations, and absorption took place only after two or three months. In 12 other cases of extrapleural blood lote formation, the coagulum was evacuated and the space was re-established by endoscopic lavage. The results were rapidly satisfactory without any untoward side effects. Streptokinase and streptodornase are indicated in cases of abundant hemorrhage and numerous clots. In 2 cases of intrapleural hemothorax following pneumonolysis, streptokinase and did not prevent pleural thickening and formation of adhesions. The results with streptokinase and streptodornase in cases of serofibrinous pleurisy were unsatisfactory, did not prevent loculation of fluid, and gave rise to particularly severe systemic reactions.—*Note sur la valeur des enzymes fibrinolytiques actuelles dans l'évolution des pneumothorax extra- et intra-pleuraux, J. Catta & J.-C. Sournia, Presse méd., July, 1952, 80: 1061.*—(*V. Leites*)

Management of Tuberculous Empyema.—Most cases of tuberculous pleural empyema develop in the course of an ineffective therapeutic pneumothorax, as was true in 20 of 22 cases. In 9, pleural involvement followed pneumonolysis; in 11, it occurred during pneumothorax. Any bronchopleural fistula should promptly be diagnosed as its presence

may threaten the patient's life. The most reliable test for this purpose is the analysis of pleural gases. In order to cure an empyema, the pus must be removed and the cavity closed. Medical treatment should control the infection. Any therapeutic pneumothorax should be discontinued immediately to prevent pleural complications if a cavity is distended by a bronchial mechanism.—*Contribucion al estudio del empiema pleural tuberculoso, V. Narvaez Obezo, Rev. tuberc., January–December, 1951, 11: 99.*—(*A. A. Moll*)

CLINICAL STUDIES, NONTUBERCULOUS DISEASES

Interstitial Giant-Cell Pneumonia.—The clinical and pathologic changes in 5 cases of interstitial giant-cell pneumonia indicate that this entity corresponds closely to the giant-cell pneumonia referred to as Hecht's disease. The chief clinical feature was rapid onset and sudden death without significant previous signs of illness. The temperature was either normal or subfebrile. Antibiotics and sulfonamides were therapeutically ineffective. The pathologic findings in the lungs consisted of congestion, patchy interstitial pneumonia, metaplastic changes, desquamation of the bronchial and alveolar lining, and the presence of epithelial giant cells with cytoplasmic inclusions. There were areas of emphysema and areas of atelectasis. In all cases the bronchial lumina contained desquamated bronchial epithelium. There seems to be some evidence in favor of viral origin of interstitial giant-cell pneumonia. This view is supported by the presence of intracellular inclusion bodies, by the epithelial proliferation and metaplasia, by the interstitial type of the pneumonia process, and by the noncontributory bacteriologic findings. This disease appears to be similar to the disease called viral pneumonia of infants, plasma-cell pneumonia, or *frühgeburten Pneumonie*, both clinically and pathologically in all respects but one, namely, the presence of giant cells.—*Studies on interstitial giant-cell pneumonia, M. Wolman, G. Izak, E. Freund, & Z. Shamir, Am. J. Dis. Child., May, 1952, 83: 573.*—(*M. J. Small*)

Endogenous Lipoid Pneumonia.—Lipoid pneumonia is generally considered to be a chronic pulmonary inflammation due to lipids of exogenous origin. The recently recognized "chronic pneumonitis of cholesterol type" may be endogenous. Focal deposits of endogenous lipids are common in the walls of lung abscesses or of bronchiectatic cavities. An endogenous lipoid pneumonia occurred frequently and unexpectedly in experimental rats during study of the toxicity of antimony trioxide. In this investigation the rats inhaled finely divided antimony trioxide particles at doses of 100 to 125 mg. per cubic meter of air for periods of two to fourteen months. Finely divided antimony trioxide induced proliferation, swelling, and desquamation of alveolar lining cells. The particles caused metabolic disturbances within macrophages and led to their fatty degeneration and necrosis. Lipids derived from such cells were demonstrable as sudanophilic droplets and as crystals, soluble in fat solvents and giving a positive reaction for steroids. These lipids from the disintegrated macrophages caused varying degrees of pulmonary fibrosis characterized by a paucity or absence of inflammatory cells other than macrophages. There was no fibrosis in lymph nodes which contained heavy deposits of antimony trioxide, indicating that the chemical did not cause pulmonary fibrosis directly. Similar pulmonary lesions, though much less severe, were produced in rats by intratracheal injection of 75 to 125 mg. of finely divided antimony trioxide in aqueous suspensions. Clinically, these results imply that other pneumoconioses may be associated with lipidic substances of endogenous origin and that certain clinical lipoid pneumonias not fully explained may be related to endogenous lipids.—*Experimental endogenous lipoid pneumonia, P. Gross, J. H. U. Brown, & T. F. Hatch, Am. J. Path., March–April, 1952, 28: 211.*—(*J. S. Woolley*)

Aspergillosis.—In 9 cases of "aspergil-

loma" located in a dilated bronchus, the only clinical symptom was recurrent hemoptysis. The roentgenographic appearance was diagnostic and unique. All cases showed a round or ovoid, homogeneous, well-defined opacity of low density surrounded on the upper three-fourths of its circumference by a radiolucent crescent-shaped zone. The outer border of this clear crescent was the bronchiectatic cavity. The surrounding parenchyma was not involved. This aspect remained unchanged during the entire observation period. The treatment of choice was segmental resection. The study was based on 5 new cases and 4 cases previously reported.—*L'aspergillome bronchiectasiant, O. Monod, G. Pesle, & Segrétain, Presse méd., November 1, 1951, 59: 1557.*—(*V. Leites*)

Pulmonary Cryptococcosis.—Because of symptoms in a woman aged fifty, roentgenograms were made and revealed a mass in the right middle and lower lobes. Bronchoscopy showed a mass just inside the orifice of the middle lobe bronchus. The bronchial biopsy and aspirate both showed typical *Cryptococcus neoformans* both morphologically and culturally. A pneumonectomy was done. The specimen showed a tumor-like mass which, histologically, was a solid mass of *Cryptococci* replacing the parenchyma. The nodes were not involved. Six days later the patient suddenly died. The cerebrospinal fluid, which preoperatively was normal, contained innumerable *Cryptococci;* these were demonstrated, but with difficulty, in the subarachnoid layers of the medulla.—*A case of pulmonary cryptococcosis, D. B. Cruickshank & G. K. Harrison, Thorax, June, 1952, 7: 182.*—(*A. G. Cohen*)

Monilial Pneumonia.—A case of pneumonia was treated with aureomycin and streptomycin when the predominant organisms were *H. influenzae* and *N. catarrhalis.* There was serious clinical deterioration. The original organisms were found to have been replaced by *Candida albicans.* All treatment with antibiotics was then discontinued and a remarkable improvement took place.—*Moniliasis pneumonia following aureomycin therapy, F. W. Wolff, Lancet, June 21, 1952, 1: 1236.*—(*A. G. Cohen*)

Pulmonary Hydatid Cyst.—In the United States, pulmonary echinococcic cyst is a disease of immigrants; residents who have never been outside of the country rarely are infected. One patient who had spent all of her life in one state did become infected. It may be significant that she had contact with numerous mongrel dogs during her childhood. A routine chest roentgenogram revealed a well-circumscribed, rounded, homogenous density measuring approximately 4 by 5 cm. and located posteriorly near the apex of the left upper lobe. This lesion was removed by segmental resection of the apico-posterior segment of that lobe. The segment contained a unilocular cystic cavity 4 cm. in diameter, filled with watery fluid and lined by a thin, pale pink, translucent membrane. This membrane stripped easily from the wall of the cyst and was dislodged as it was opened. Numerous scolices, many of which had hooklets, were found in the alveoli immediately adjacent to the cyst. The morphology of the scolices was typical of *Echinococcus granulosus.*—*Pulmonary hydatid (echinococcic) cyst: Report of native case, J. H. Johnston, Jr., & G. E. Twente, Ann. Surg., August, 1952, 136: 305.*—(*M. J. Small*)

Pulmonary Echinococcus.—Ten cases of *Echinococcus* cysts of the lung, 4 of them treated by the author, illustrate that the second most common localization of cysts, after the liver, is the lung, which may contain a small or large clear cyst. When the cyst is large, the roentgenogram is often diagnostic, whatever the result of the skin test. These large clear cysts are treated by cystectomy, with or without marsupialization. The author uses local anesthesia and closes the wound without drainage, closure by primary intention being possible with antibiotic therapy. The cysts which have become complicated, as by bronchiectasis, require more extensive operation.—*A propos de dix cas d'échinococ-*

case pulmonaire, J. Papadopoulos, Poumon, April, 1952, 8: 300.—(F. S. Lansdown)

Pulmonary Changes in Uremia.—In a series of 8 cases of "uremic lungs", the roentgenographic findings were usually extensive densities confined to the inner lung zones. Occasionally there was involvement of the basal portions. On pathologic examination, no evidence of infection or arteritis was found. Hyaline membranes and hyaline deposits in the alveoli were common features. These changes were most striking in cases associated with acute episodes of glomerulonephritis. They are not specific and are also found in other conditions with altered pulmonary capillary permeability.—*Pulmonary changes in uremia, J. E. Bass, D. Greenberg, E. Singer, & M. A. Müller, J. A. M. A., March 1, 1952, 148: 724.—(H. Abeles)*

Atelectasis of Middle Lobe.—During five years, 40 cases of post-tuberculous or nonspecific bronchial stenosis were seen. Among these, middle lobe involvement was observed in 19, 7 being clearly post-tuberculous, 5 definitely nonspecific, and 7 possibly either. The criteria used were the tuberculin test and the presence of calcified nodes. A history of frequent colds was obtained in 9 and of pneumonia in 7. Chronic cough was present in 11, hemoptysis in 7, abundant expectoration in 5, and right anterior chest wall pain in 3. Bronchoscopy showed stenosis of the orifice of the middle lobe bronchus in only 4 cases and congestion and edema of the mucosa of the ostium in 7. In 8, there were negative findings. The lateral roentgenogram showed the changes of atelectasis more satisfactorily than the anteroposterior view. In 6 cases, calcified lymph nodes were seen. Lateral tomograms showed stenosis of the middle lobe bronchus in 10 cases; in most cases, the constriction was situated 1 to 2 cm. from the bronchial orifice. Bronchiectasis was demonstrated by tomography in 10 cases. Bronchography rarely was necessary. Operation was performed in 9 cases; middle lobe lobectomy was performed in 8 cases and pneumonectomy in one. Pathologic study showed atelectasis, chronic inflammation, and bronchiectasis in every case. A lymph node adherent to the middle lobe bronchus was found in 4 cases. There were no operative fatalities or serious complications. Five of 6 patients re-examined are well. Ten patients were treated conservatively and have remained well.—*The so-called middle lobe syndrome, B. Fretheim, Thorax, June, 1952, 7: 156.—(A. G. Cohen)*

Chronic Segmental Atelectasis.—Chronic segmental atelectasis, which is common in children, is as important and not at all unusual in adults. In a series of 12 patients, aged seventeen to seventy years, tuberculosis was demonstrated by culture in 5 and all had calcified hilar lymph nodes. Of these 12 patients, 8 dated the apparent onset of atelectasis to an acute episode of bronchial or pulmonary infection. Atelectasis was prolonged in each instance, re-expansion always requiring six weeks or longer. Another 4 patients were not included because atelectasis persisted only approximately three weeks. The predominant symptom was chronic, usually productive, cough. Bronchoscopies revealed normal findings in 5 of the 12 patients, no evidences of extrinsic bronchial compression being noted. Therapy was conservative, surgery being advised for only 2 patients and performed in only one.—*Chronic segmental atelectasis, W. R. Beisel & J. O. Gillespie, U. S. Armed Forces M. J., March, 1952, 3: 407.—(E. A. Rouff)*

Pulmonary Thrombo-Embolism.—Pulmonary thrombo-embolism was diagnosed during a period of thirty months in 120 patients, of whom 113 were in the wards of a general hospital. The incidence of pulmonary thromboembolism in this hospital was higher than that of lobar pneumonia. Pulmonary embolism was directly responsible for 30 deaths, and pulmonary infarction was an important contributory factor in 13 more. Fifty-eight per cent of the cases were classed as medical, and 80 per cent of these had heart disease. There were 3 instances (one fatal) of pulmonary embolism

appearing without warning in apparently healthy subjects. Among the 30 surgical cases (8 fatal) were 4 in which pulmonary embolism was precipitated by first rising. Among the 20 obstetrical cases (2 fatal), pulmonary embolism was nearly three times as common in those over the age of thirty as in those under thirty. Pulmonary embolism was only once seen in the absence of obvious femoral thrombosis or some complication of pregnancy or delivery. Pleuritic pain and hemoptysis are the 2 most striking symptoms of pulmonary infarction. Pleuritic pain was noted in 65 per cent of all cases and was present in fully 90 per cent of the surgical and obstetrical cases. Hemoptysis was noted in less than 40 per cent of all cases; the incidence falls to 17 per cent if cases with heart disease are excluded. The physical signs in the chest in pulmonary infarction depend on the presence and degree of three factors, namely, consolidation, pleurisy, and elevation of the diaphragm. Signs of pleural effusion were present in 20 per cent of cases. The fluid was blood-stained in 8 of 17 cases in which it was suspected. Jaundice was observed in almost one-third of the cases of heart disease complicated by pulmonary infarction. A paroxysm of auricular fibrillation was precipitated by pulmonary infarction in 5 cases. In several patients with congestive heart failure the symptoms were slight and the presence of pulmonary infarction was overlooked. In postoperative and puerperal patients the condition was often misdiagnosed as pleurisy, pulmonary collapse, or pneumonia. Paying serious attention to every case of femoral thrombosis and pulmonary embolism is important (Author's summary).—*A survey of pulmonary embolism in a general hospital, D. S. Short, Brit. M. J., April 12, 1952, No. 4762: 790.*—(*E. A. Riley*)

Fatal Pulmonary Embolization.—Among 29,383 autopsies done at the Vienna University Pathological Institute between the years 1941 and 1951, there were 487 cases (1.6 per cent) of fatal pulmonary embolisms. The incidence of 1.3 per cent in 1941 decreased to 0.4 per cent in 1945 and increased after the war to 4.4 per cent in 1948 and 4.9 per cent in 1949. The decrease and increase were similar in both sexes. In central Europe during the past sixty years, the incidence of embolism has been high when economic conditions were good, and low when they were poor. Of the cases of fatal pulmonary embolisms, 63.2 per cent occurred in persons more than sixty years old but the recent increase in the number of cases is not explained by the increased age of the population. Embolism was considerably more frequent in well-fed individuals than in poorly nourished persons; the improved nutritional status in the last years seems to be a factor in the increased incidence. Fatal embolism was three times as frequent in women as in men and was observed following surgery approximately as often as in internal diseases.—*Untersuchungen über fulminante, tödliche Lungenembolien am Obduktionsmaterial der Jahre 1941 bis 1951, J. Zeithofer & G. Reiffenstuhl, Wien. klin. Wchnschr., June 20, 1952, 64: 446.*—(*G. C. Leiner*)

Respiratory Infections in Poliomyelitis.—Patients with a severe degree of residual paralysis of the respiratory muscles after poliomyelitis present a considerable problem during the winter months. Minor respiratory infections may quickly involve the bronchi with resultant collapse of a segment, lobe, or lung. In an attempt to avoid the necessity for bronchoscopy, the following routine was adopted: (*1*) In all severely paralyzed cases, chest films in both inspiration and expiration are taken on admission; the vital capacity is also determined. (*2*) All cases with even slight respiratory infections are reported to the physician immediately. (*3*) Penicillin therapy is started at once. (*4*) Cultures of the nose and throat are taken. The physiotherapists have been taught to recognize the presence of accumulations of mucus in the bronchial tubes and of pulmonary collapse. The earliest stage is characterized by accumulation of excess mucus in the bronchial tree and often lasts from seven to twenty days. The physiotherapist must then see the patient four or

more times a day. The patient is encouraged to cough, and simultaneously the therapist presses the front and back of the chest together. Clearing of bronchial blockage requires immediate treatment. Pulmonary collapse beyond the blockage is evidence of failure, and bronchoscopy must be performed.—*Management of respiratory infections in patients severely paralysed by poliomyelitis, F. H. Stevenson, Lancet, April 26, 1952, 1: 845.*—(*A. G. Cohen*)

Neonatal Pulmonary Cystic Disease.—Congenital cystic disease of the lung may be a surgical emergency in the newborn. Respiratory distress is striking and appears in either an immediate or a delayed postnatal form. In the immediate form, spontaneous breathing is retarded and vigorous resuscitative measures often are necessary; in the delayed form, distress is not evident for several hours or days after birth. Diagnosis is easy if chest roentgenograms are obtained routinely in cases of neonatal respiratory distress. The characteristic finding is a giant cyst filled with air which displaces the mediastinum. Conditions to be differentiated in the diagnosis are agenesis of the lung, spontaneous pneumothorax, and congenital diaphragmatic hernia. The treatment of choice is radical extirpation of the diseased lung by lobectomy or pneumonectomy, both of which are well tolerated even in the first few days of life. A seven-day-old infant, treated by left lower lobectomy, is believed to be the youngest patient with pulmonary cystic disease to have had a successful pulmonary resection.—*Congenital cystic disease of the lung in the newborn: Report of a successful left lower lobectomy in a seven-day-old infant, F. B. Whitesell, Jr., & W. J. White, Ann. Surg., August, 1952, 136: 299.*—(*M. J. Small*)

Phrenic Rebound Phenomenon.—A new physical sign has been found in cases of intraperitoneal hemorrhage and of peritonitis. This consists of the production of abdominal pain by pressure on the phrenic nerve in the neck. The sign is elicited by turning the patient's head towards the contralateral side, and applying pressure at a point approximately one inch above the clavicle, just posterior to the lateral border of the sternocleidomastoid muscle. The abdominal pain produced is sharp, sudden, and cramping, most frequently located at the lateral border of the rectus abdominis muscle. This sign was absent in numerous acute intra-abdominal conditions not accompanied by hemoperitoneum and peritonitis.—*The phrenic rebound phenomenon—a new physical sign, E. Hoffman, Ann. Surg., August, 1952, 136: 316.*—(*M. J. Small*)

Cough-Suppressing Drugs.—A method was devised of producing cough by spraying the larynx with irritant solutions. All investigations were carried out on the same subject, a man aged forty-two, who could tolerate the sprayer in his pharynx for long periods of time. The efficiency of codeine, morphine, heroin, and amidone in suppressing cough were assessed. Heroin was the most efficient cough-suppressant for both strong and weak stimuli. Morphine and amidone were highly effective. Codeine did not appear to have any suppressive value. The psychological factor played a role in all of the experiments.—*The assessment of cough-suppressing drugs, B. R. Hillis, Lancet, June 21, 1952, 1: 1230.*—(*A. G. Cohen*)

Bronchogenic Carcinoma.—The incidence of bronchogenic carcinoma is increasing more rapidly than that of any other cancer. There is a causal relationship between this increased incidence of bronchogenic carcinoma and the increased use of cigarettes. It is primarily a disease of men, probably because the bronchial mucosa in men is more susceptible to malignant change than in women. It is more frequent in white men than in Negroes and is primarily a disease of older persons. In a series of 948 cases of bronchogenic carcinoma, resection was possible in 332 cases. Of the resected cases, 49.5 per cent were epidermoid, 30.5 per cent were undifferentiated, and 20 per cent were adenocarcinomas. Epidermoid

carcinomas were infrequent in women, but adenocarcinomas occurred relatively more frequently in women than in men. These adenocarcinomas were more often in the periphery and their relative incidence decreased with advancing age; whereas the incidence of epidermoid carcinoma increased with advancing age. The latter is probably due to the carcinogenic effect of tobacco over a longer period. Adenocarcinomas probably originate in embryonic rests and they become evident, therefore, at an earlier stage. Their incidence is not affected by smoking. In the cases in which resection was done, a bronchogenic carcinoma was suspected roentgenographically in 84 per cent. A diagnosis of carcinoma was made bronchoscopically in only 38 per cent of the cases. Cytologic examination of sputum or bronchial secretions indicated cancer in 68 per cent of 112 cases examined by this method. The treatment of bronchogenic carcinoma is pneumonectomy with complete en bloc removal of all of the mediastinal nodes. Paralysis of the phrenic nerve or recurrent laryngeal nerve was not considered a contraindication to exploratory thoracotomy. Of the 332 patients in whom resection was done, 20 per cent died in the hospital. In 232 patients the resection was termed a palliative one, which means that the tumor had extended beyond the lung. Of 948 patients, only 59 per cent were operable, 35 per cent were resectable, 28 per cent survived resection, and only 6 per cent were alive at the end of five years. Of the patients in whom palliative resection was done, 10 per cent were alive at the end of five years, compared with 38 per cent of those in whom curative resection was done. None of the patients without resection survived five years.—*Bronchogenic carcinoma, its frequency, diagnosis, and early treatment, A. Ochsner, P. T. DeCamp, M. E. DeBakey, & C. J. Ray, J. A. M. A., March 1, 1952, 148: 691.—(H. Abeles)*

Excision of Metastatic Tumors.—Pulmonary metastasis of a visceral carcinoma or sarcoma may appear as a single rounded mass simulating peripheral primary bronchopulmonary cancer. The late appearance of this metastasis, several years after the satisfactory ablation of the primary tumor, may be an indication for pulmonary resection. The primary tumor is often a genitourinary or digestive cancer. In 6 cases there were 4 genital cancers, one hypernephroma, and one cancer of the colon. The results of the surgery are encouraging: 3 patients survived more than two years, 2 having survived more than three years. Among the metastatic tumors, adenocarcinomas and sarcomas are relatively frequent. Their discovery in the course of the examination of an isolated peripheral pulmonary lesion indicates the need for routinely considering the possibility of a metastasis (Author's summary).—*L'exérèse des tumeurs métastatiques pulmonaires à type de masse périphérique isolée, P. Santy, P. Galy, Larbre, & Bethenod, Poumon, April, 1952, 8, 283.—(F. S. Lansdown)*

Intrathoracic Duplications of Alimentary Tract.—A review of the findings in 6 cases and the detailed description of another case form the basis for suggesting that intrathoracic duplications of the alimentary tract communicating with the small intestine be added to the list of possible causes of 2 groups of symptoms and signs in infants and young children. In one group respiratory symptoms and signs of cyanosis, dyspnea, cough, and chest pain are produced by pressure of the bulbous intrathoracic portion of the duplication distended with gas and fluid. In the other group, abdominal pain, gastrointestinal hemorrhage, and anemia result from ulceration of, and hemorrhage from, the gastric mucosa that forms the lining of some of these duplications. The presence of such a duplication is suggested on roentgenographic examination of the chest by a soft tissue mass, frequently containing air or fluid. Proof of a duplication is established on roentgenographic examination, using barium, by the presence of a single channel communication between the thoracic mass and the intestine. Operative intervention is the only rational treatment. Of the 7 known cases, 2 patients died in the immediate post-

operative period and the remaining 5 have been relieved of symptoms (Authors' summary).—*Intrathoracic duplications of the alimentary tract communicating with the small intestine, J. E. Davis & W. A. Barnes, Ann. Surg., August, 1952, 136: 287.—(M. J. Small)*

Tracheo-esophageal Fistula.—Excessive amounts of saliva and frothy mucus at the mouth of a newborn baby suggested a tracheo-esophageal fistula and a No. 8 French catheter was inserted into the esophagus. Since an obstruction was met, roentgenographic studies with iodized oil were done confirming the diagnosis of fistula. Ligation of the fistula with primary end-to-end anastomosis of the esophagus was performed when the patient was little more than six hours old. The post-operative course was exceptionally smooth and oral feeding was started thirty-six hours after the operation.—*Tracheo-esophageal fistula, value of immediate diagnosis, with report of a case, G. N. Weiss & C. J. Miangolarra, J. A. M. A., March 1, 1952, 148: 732.—(H. Abeles)*

Pleural Space After Pneumonectomy.—Complications resulting from the residual pleural cavity after pneumonectomy for tumor are primarily mechanical; after pneumonectomy for tuberculosis they are chiefly infectious. Fibrin is a fragile prosthesis, liquefies easily, and poses little barrier to infection. Packing the pleural space with foreign material merely reduces it, the interstices becoming filled with fibrin. For this reason the author resects the entire pleura at the time of pneumonectomy. Two weeks later an extramusculo-periosteal pocket is created and filled with prosthetic material. This effectively effaces the original cavity and brings soft tissue against the mediastinum where the absence of pleura favors cicatrization. The prosthetic material is at a distance from the mediastinum and the integrity of the external thorax is retained.—*Une technique d'effacement de la cavité restante après pneumonectomie, M. Hertzog, Poumon, April, 1952, 8: 319.—(F. S. Lansdown)*

Paraffin Filling After Pneumonectomy.—Complications from mediastinal shift and/or infection of the pneumonectomy space, with or without bronchopleural fistula, occurred after pneumonectomy in 4 patients with primary malignancy of the lung and in 2 with nonspecific inflammatory disease. The pleural space was obliterated in 3 patients by extrapleural paraffin plombage. In 2 patients, an empyema cavity was obliterated by a limited thoracoplasty combined with a subscapular paraffin pack following drainage of the empyema. In the remaining case of empyema, extrapleural paraffin plombage with thoracoplasty following drainage was utilized. The results were satisfactory in all 6 patients.—*The use of paraffin as an aid in obliterating the pleural space following total pneumonectomy, W. E. Adams & J. M. Fritz, Ann. Surg., July, 1952, 136: 18.—(M. J. Small)*

Angiocardiography of Asthma.—Angiocardiograms of 38 patients with varying degrees of bronchial asthma showed that all had fever and smaller than normal distal branches of their pulmonary arteries. The arterial circulation was much slowed. It was reduced progressively and at first intermittently at the time of the attacks; it was permanently reduced in severe status asthma. In terminal stages of cor pulmonale, large areas of the lung were almost completely avascular. As the distal arterial tree diminished, the trunks and the proximal branches dilated. The extent of distal arterial vasoconstriction depended on the gravity and duration of the respiratory disturbance.—*La circulation artérielle pulmonaire chez les asthmatiques sous l'angle de l'angiocardiographie, L. Stuhl, P. Maurice, L. Scebat, P. Y. Hatt, & J. P. Sebillotte, Semaine d. hôp. Paris, January, 1952, 28: 84.—(V. Leites)*

Left Coronary Artery from Pulmonary Artery.—The left coronary artery arose anomalously from the pulmonary artery in a four-month-old girl. Patients with this rare anomaly usually do not survive the first year of life, although a few have lived to

adulthood. In infancy there is progressive dyspnea, apparent pain and symptoms of shock after feeding, and progressive cardiac enlargement and failure. Cyanosis, clubbing, cardiac murmurs, and thrills are absent. The electrocardiogram shows inversion of T waves, usually in all three limb leads, and low voltage. Roentgenograms and fluoroscopy reveal conspicuous cardiac enlargement, primarily to the left.—*Origin of the left coronary artery from the pulmonary artery, H. Hartenstein & J. Freeman, A. M. A. Am. J. Dis. Child., June, 1952, 83: 774.*—(*M. J. Small*)

ANTIMICROBIAL THERAPY

Isoniazid Resistance.—That bacterial resistance to isoniazid develops *in vivo* is demonstrated by a streptomycin-resistant patient with active tuberculosis who received 250 mg. of isoniazid daily for sixty days. Tubercle bacilli recovered at the end of that period were resistant to 20 γ of isoniazid per ml. Initially, the volume of sputum expectorated decreased from 50 to 20 cc. daily and contained fewer tubercle bacilli; later the volume and bacillary content of the sputum increased. Another patient who died of pulmonary tuberculosis after twenty-eight days of treatment with isoniazid had tubercle bacilli resistant to 10 γ of isoniazid per ml. In addition to these 2 patients, isoniazid-resistant bacilli appeared after thirty days of treatment in 7 other cases. Follow-up studies are being carried on to determine whether or not sensitivity to isoniazid returns after the drug has been discontinued.—*Apparition de B. K. résistant au Rimifon chez un malade traité par ce medicament, G. A. Nigoghossian, Schweiz. med. Wchnschr., July, 1952, No. 27: 707.*—(*E. Dunner*)

Isoniazid Resistance.—The patient's clinical course during isoniazid therapy paralleled the sensitivity or resistance of his tubercle bacilli to isoniazid. Isoniazid resistance of the bacilli from 2 patients also paralleled resistance to iproniazid (isonicotinyl isopropyl hydrazine). This resistance developed within a four-week treatment period. Of 40 patients treated with isoniazid, 5 patients, after sixty-two days of treatment, had bacilli resistant to 5γ per ml. and sensitive to 50γ per ml; 12 patients, after sixty-one days of treatment, had tubercle bacilli which were sensitive to 0.5γ per ml. and resistant to 5.0γ per ml. After a thirty- to ninety-day treatment period, studies showed no change from the initial sensitivity to 0.5γ per ml. in 23 patients.—*Erste Beobachtungen von Rimifon-Resistenz, E. Wiesmann, J. Wanner, & E. Tanner, Schweiz. med. Wchnschr., August 2, 1952, No. 31: 785.*—(*E. Dunner*)

Clinical Use of Isoniazid.—A series of 100 pulmonary and 14 extrapulmonary cases of active tuberculosis were treated with 3.5 to 4 mg. of isoniazid per kg. of body weight daily for four to ten weeks. The tentative impression of the chest roentgenograms after this short period of therapy was that 74 cases remained unchanged, 17 had improved, and 9 appeared worse. Bacteriologically, one-third of the patients whose sputum concentrates had contained tubercle bacilli produced negative concentrates during therapy. There was an important discrepancy between the roentgenographic and bacteriologic changes in that several patients produced sputum negative for tubercle bacilli despite unchanged and even progressive roentgenographic findings. Isoniazid-resistant bacilli appeared in one patient after four weeks of treatment. Favorable changes in the mucosa were noted in several patients with tuberculosis of the urinary bladder and larynx. Increased appetite, weight gain, and decreased cough and expectoration may be nonspecific therapeutic effects. Metabolic and glandular disturbances were not observed. Complications consisted of exudative reactions with temperature elevation, leukocytosis, increased auscultatory findings, increased expectoration, and exudation into the pleural space. Drug fever occurred in one patient. The optimum dose and duration of therapy is not known as yet. Isoniazid therapy does not abolish the necessity for surgical intervention.—*Rimifon in der Behandlung der Tuberkulose: erste klinische*

Beobactungen, E. Tanner, J. Wanner, H. Wehrlin, & Z. Ramer, Schweiz. Ztschr. f. Tuberk., 1952, No. 4: 255.—(E. Dunner)

Clinical Use of Isoniazid.—A series of 66 patients with active pulmonary tuberculosis and 5 with meningitis have completed at least four weeks of treatment with 300 mg. of isoniazid daily. This series was comprised of 47 men and 24 women, from eleven to sixty-five years old, with cavitary disease. Transient vertigo appeared in only a few cases; obstipation was present in 5. The obstipation responded well to injections of prostigmine. Urinary complications were manifested in but one patient. Appetite improved in 51 cases, remained unchanged in 12, and diminished in 3. Weight increased in 57 and decreased in 9. Expectoration diminished in 44 cases, remained unchanged in 21, and increased in one. The sedimentation rate decreased in 43, remained unchanged in 9, and increased in 14. A change from sputum positive for tubercle bacilli to negative was reported in 53 per cent of the cases. Roentgenographic improvement was noted in 20 of the 66 cases. Of the 5 patients with tuberculous meningitis, 2 were adults and 3 were children. From 6 to 12 mg. of isoniazid, administered intrathecally, was well tolerated. Clinical improvement was remarkable from the first week. In each case the spinal fluid sugar increased and the albumin decreased. It is concluded that isoniazid is efficacious in the treatment of many patients who did not respond to previous antimicrobial therapy or collapse measure.—*Premières observations de malade traités par un nouvel agent chimique, J. Morin, Schweiz. Ztschr. f Tuberk., 1952, No. 4: 243.—(E. Dunner)*

Clinical Use of Isoniazid.—A series of 55 patients with active tuberculosis received 5 mg. of isoniazid per kg. of body weight daily during five months. In several cases the dosage was increased to 8 to 10 mg. per kg. No other antimicrobial agent was used during this treatment period. Observations on the patients' temperature, weight, roentgenographic changes, blood picture, and sputum findings indicated definitely that there was evident antituberculous activity and that toxic manifestations during a five-month treatment period, using a 5 mg. per kg. dose, were minimal and of no consequence. During isoniazid therapy, defervescence was not by crisis but was gradual over a one- to two-week period. Weight gain was striking. During the first two months, one-third of the patients gained 5 to 10 kg. and another third gained 3 to 5 kg.; one patient gained 17 kg. The weight was maintained through the fourth month. This weight gain served as a markedly favorable psychological stimulus. It occurred both in the caseous exudative cases and in the chronic productive type of case. In contrast to other oral medication, isoniazid was well tolerated and stimulated the appetite, especially during the first few weeks of treatment. There was a tendency towards decreased expectoration in two-thirds of the patients with cavitary disease. In 8 of 29 patients with cavitary disease, the sputum became free of tubercle bacilli within a two- to four-month period. Cough became less frequent in two-thirds of the cases. In general, the chest roentgenograms showed a tendency to improve; no new areas of infiltration appeared. As a rule no effect on the sedimentation rate was noted during the first four weeks; it decreased by the end of the second month of treatment. In comparison with other antimicrobial agents, isoniazid was thought to be better than *p*-aminosalicylic acid but not more effective than streptomycin. Isoniazid resistance appeared in one case following twelve weeks of treatment (Authors' summary).—*Chemotherapie der Tuberkulose mit Rimifon (Isonicotinylhydrazin), M. Engel & O. Gsell, Schweiz. med. Wchnschr., August 16, 1952, No. 33: 825.—(E. Dunner)*

Isoniazid in Rabbit Eye.—The anterior chamber of the right eye of 52 rabbits was inoculated with a suspension containing 0.1 mg. of virulent tubercle bacilli. In order to test the efficacy of isoniazid, the animals were divided into four groups: (*1*) untreated controls, 10 rabbits; (*2*) treated with isoniazid,

20 rabbits; (*3*) treated with isoniazid and streptomycin, 11 rabbits; (*4*) treated with isoniazid, streptomycin, neomycin, terramycin, and *p*-aminosalicylic acid (PAS), 11 rabbits. When isoniazid was administered alone, 10 mg. per kg. daily were used; when the drug was used with other agents, 6 mg. per kg. daily were given. Streptomycin, neomycin, terramycin, and PAS were administered in large doses. Treatment was begun twenty-four hours after infection. When treated with isoniazid only, one animal developed signs of ocular inflammation. On the twenty-fifth day, treatment of 12 rabbits was discontinued. During the ensuing twenty days, they showed no pathologic changes nor did the 8 animals still being treated. From the group of control rabbits, 4 were started on treatment fifteen days after infection, at which time there was florid evidence of tuberculous changes. The treated lesions regressed rapidly. With combined therapy, there was no sign of inflammation at the twentieth day. The histology and bacteriology of this experimental therapy is being studied.—*Studio sulla chemioterapia della tuberculosi: Idrazide dell'acido isonicotinico ed associazioni chemio-antibiotiche nella tuberculosi oculare sperimentale, G. Lepri & S. Catalfi, Minerva med., May 24, 1952, 43: 1113.*—(*L. B. Hobson*)

Action of Isoniazid.—*M. tuberculosis*, strain H37Rv, showed complete bacteriostasis when exposed to 5 to 10γ of isoniazid per ml. of Dubos medium. Mice infected with 2 mg. of H37Rv received a total of 46.5 mg. of isoniazid in daily doses of 0.5 to 1.5 mg. The animals were sacrificed on the thirty-eighth day. All of the untreated control mice died between the twenty-second and thirty-first days. There were extensive tuberculous lesions in the lungs; the spleen, liver, and kidneys were less involved. Of the treated mice, 25 per cent died between the twenty-third and thirty-seventh days due to an unidentified viral infection, not tuberculosis. Among the surviving animals, 75 per cent had only slight tuberculous changes in the organs. In 25 per cent, no tubercle bacilli could be demonstrated in the lungs; in the other mice, only one or two bacilli were seen in an entire slide. The kidneys showed no evidence of tuberculosis.—*Activité antituberculeuse de l'isonicotinhydrazide (INH), C. Levaditi, A. Vaisman, & H. Chaigneau-Evhard, Ann. Inst. Pasteur, July, 1952, 83: 127.*—(*V. Leites*)

Isoniazid Effects in Vitro.—The bacteriostatic and bactericidal effects on tubercle bacilli were studied, using 9 concentrations of isoniazid (isonicotinic acid hydrazide) ranging from the bacteriostatic dose of 0.1γ per ml. to 1,000γ per ml. After exposure to these concentrations, cultures on Jensen's medium and 27 guinea pig inoculations were made. After twenty-four hours of contact with any concentration of isoniazid, tubercle bacilli grew in ten days; after forty-eight hours of contact, concentrations above 50γ inhibited viability; after one week of contact with any concentration, no bacilli could be cultured. Even after one week of contact with 1 mg. per ml., the bacilli remained virulent for the guinea pig. No morphologic alterations of the tubercle bacilli could be demonstrated with Fontes' staining method.—*Dissociation de pouvoirs bacteriostatiques et bactericide de l'hydrazide isonicotinique in vitro, F. Tison, Ann. Inst. Pasteur, July, 1952, 83: 134.*—(*V. Leites*)

Effect of Isoniazid.—Isoniazid acts very effectively *in vitro* on the tubercle bacillus, since after ten days cultures are inhibited by a dilution of 10^{-8}. This cannot be considered a bactericidal effect, however, because during the ensuing days cultures appear in lower dilutions; after one month the bacilli can be grown at titers below 10^{-6}. Isoniazid and *p*-aminosalicylic acid (PAS) are definitely synergistic, especially in the proportion of one part of isoniazid to 100 parts of PAS. A bactericidal effect is produced by 1:2,000,000 PAS with the 1:200,000,000 isoniazid (Author's summary).—*Action in vitro de l'hydrazide de l'acide isonicontinique seul et combiné avec d'autres produits, Mme. Aïtott, Ann. Inst. Pasteur, July, 1952, 83: 130.*—(*V. Leites*)

Streptomycin Resistance in Meningitis.—Among 510 children hospitalized with tuberculous meningitis between 1947 and 1951, 24 streptomycin-resistant strains were found. This figure is considered to be less than the real incidence of streptomycin resistance, partly because the frequency of examinations was limited by the existing laboratory facilities, especially in the early part of the study. Of the 90 patients hospitalized between January, 1950, and June, 1951, 13 had streptomycin-resistant strains, 6 were resistant at the onset of meningitis, 18 became resistant during treatment. Two of the patients with initial resistance to streptomycin had received the drug on previous occasions; the remaining 4 children had never been treated with streptomycin. Five of these 6 children died of tuberculous meningitis after twelve to twenty-two days. Sixteen patients developed resistant strains while the disease was becoming chronic and more severe. In 2 cases, resistant strains were found at the onset of a late relapse.—*Bacilles résistants à la streptomycine dans la meningite tuberculeuse, R. Debré, H. E. Brissaud, & C. H. Noufflard, Semaine d. hôp. Paris, May, 1952, 28: 1676.*—(*V. Leites*)

Tuberculous Meningitis in Children.—From November, 1947, to the end of December, 1950, 114 children with tuberculous meningitis were treated with streptomycin in the Department of Pediatrics of the University of Vienna. As of January 1, 1952, 60 children (52.6 per cent) were living, following treatment instituted twelve to forty-nine months previously. The intramuscular dose of streptomycin was 40 mg. per kg. daily, or as much as 2 gm. At present this dose is divided into five daily injections and continued until recovery is achieved. When the cerebrospinal fluid is normal, the dosage is reduced to 30 mg. per kg. and, after another two to four weeks, to 20 mg. per kg. If no complications ensue, all intramuscular administration is discontinued after one to two months on the latter dosage. The intrathecal dose is 2 mg. per kg. daily for one week, patients with increased cerebrospinal fluid pressure receiving half of this dose twice daily. After the first week, 1 mg. per kg. once a day is given until the fluid shows definite improvement. Thereafter, depending upon cerebrospinal fluid findings, the dosage is reduced at intervals of weeks to every second day, every third day, and every week. The glucose content of the fluid first becomes normal, then the number of cells, and finally the protein content. Intrathecal treatment must be given until the cerebrospinal fluid is completely normal and is continued until it remains normal for one to two months. Following this, the fluid is examined every eight to fourteen days without intrathecal injections. The average period of intramuscular therapy has been five to ten months; and of intrathecal therapy, three and one-half to eight months, each child receiving thirty to ninety injections. The younger the child the greater was the mortality; after the fourth year of life the prognosis improved considerably. The prognosis in children with meningitis alone was slightly better than in those who had miliary tuberculosis but the difference was not significant. Streptomycin-resistant bacilli were never observed. With the treatment schedule described, no relapse has occurred. In 40 children streptomycin therapy was combined with thiosemicarbazone. Of these, 33 were alive and completely cured; only 7 died. This combined therapy is considered especially effective. Most patients who recovered had no severe psychic or neurologic sequelae.—*Tuberculous meningitis, O. Ruziczka, J. Pediat., June, 1952, 40: 708.*—(*M. J. Small*)

Tuberculous Meningitis.—Between 1947 and 1950, 95 patients between the ages of fourteen and forty-eight years were treated for tuberculous meningitis. Of these, 63 were less than twenty years old. The meningitis was associated with miliary tuberculosis in 29.5 per cent of the cases and with nonmiliary pulmonary lesions or extrapulmonary tuberculosis in 28.5 per cent. Various treatment regimens were carried out in successive years. The best results were obtained in 1948 to 1950 with daily administration of 1 gm. of

streptomycin intramuscularly for at least six months and 0.1 gm. intrathecally daily during the first six weeks and then every other day for ten weeks. Daily intramuscular doses of 2 and 3 gm. were used in 1947. At the time of writing, 42 (44 per cent) of the 95 patients had survived. The observation period was more than twenty-four months in 22 cases, eighteen to twenty-four months in 6 cases, and twelve to eighteen months in 14 cases. All of these patients had been discharged and several of them had returned to work. Only one patient had neurologic sequelae with paralysis of eye muscles. No psychic disturbances were noted in the 42 convalescents. All had more or less marked vestibular damage, as well as considerable impairment of hearing for high frequencies; 10 of the 42 were completely deaf. During the first month of therapy 21 patients died; in all of these, treatment was instituted too late. Another 25 had either initial improvement, with subsequent exacerbation and death, or a chronic downhill course with death in a state of cachexia. Of 14 patients who relapsed, 7 died. In most cases, relapse occurred within three months of discontinuance of treatment. Relapse was less frequent with the most recent regimen. The following factors were unfavorable prognostically: (*1*) age: survival was 47 per cent in the age group 14 to 20, 60 per cent in the age group 20 to 25, and 16 per cent in the group older than 25; (*2*) comatose state on admission; (*3*) delay of treatment for more than two weeks after onset of first symptoms; (*4*) cerebral localization; and (*5*) persistence of psychic disturbances after one month of treatment. When tuberculous meningitis was associated with miliary tuberculosis and visible choroid tubercles, the meningeal process followed direct hematogenous dissemination and probably was identical with the process in the lungs. Such disease had a better prognosis than meningitis originating in a larger caseous focus of the cerebral cortex. —*Résultats du traitement de la meningite tuberculeuse par la streptomycine chez l'adolescent et l'adulte, P. Regniers, K. Vuylsteek, J. M. Verstraeten, B. De Landsheere, & R. Wilme, Semaine d. hôp. Paris, April, 1952, 28: 543.—(V. Leites)*

Treatment of Tuberculous Meningitis in Children.—During the past four and one-half years, 26 infants have been treated at the Los Angeles Children's Hospital for tuberculous meningitis; 15 additional patients had miliary tuberculosis. Tubercle bacilli were isolated from the cerebrospinal fluid of 25 patients during life and from the meninges of the other patient at autopsy. The diagnosis was confirmed by autopsy of 12 of the 19 patients who died. The meningitis has been arrested in 7 infants for periods between twenty and forty months following the institution of therapy; 2 show no demonstrable neurologic or intellectual sequelae; 3 are mildly retarded mentally but currently show steady improvement; and 2 show marked mental deterioration. Neither the promptness with which treatment was started, the presence of miliary tuberculosis, nor the use of intrathecal streptomycin influenced the outcome. All of the 15 infants and children treated for miliary tuberculosis alone received streptomycin and 8 were given additional tuberculostatic drugs. Each patient had typical roentgenographic changes in the lungs and a positive Mantoux test; tubercle bacilli were isolated from 12 of these patients and, during a later episode of meningitis, from one other. Only one patient, who was moribund when treatment was started, succumbed promptly to the infection. In 14 patients, the miliary tuberculosis was arrested; 7 are in good health from sixteen to sixty-one months later; one boy has active bone tuberculosis, 3 still have active pulmonary tuberculosis, one died of a progressive primary tuberculosis, and 2 later died of tuberculous meningitis. Two patients developed benign serous tuberculous meningitis with only lymphocytic pleocytosis during the course of their miliary disease. Infants aged four months to four and one-half years were given intramuscular streptomycin averaging 1.0 gm. daily, usually in a single dose. Streptomycin every other day often was continued after discharge. Higher daily doses or

more frequent injections gave no more favorable results. Patients whose meningitis was arrested received intramuscular streptomycin for three to seven months. Intrathecal streptomycin was given to the 15 more gravely ill patients in doses of 20 to 50 mg. without demonstrable effect on the outcome. Promizole was used in daily doses of 3 to 4 gm., serum levels of 1 to 4 mg. per 100 cc. being obtained; 6 patients received this drug continuously for fifteen to thirty-five months. Three patients were given neomycin B in addition to streptomycin, with no favorable effect. *p*-Aminosalicylic acid (PAS) and amithiozone were given to a few patients who received streptomycin and Promizole. Meningitis recurred during Promizole therapy in 3 of 8 patients whose initial attack had been arrested. Continuing Promizole after tuberculous meningitis is arrested does not guarantee against recurrence. All patients treated for six weeks or more with streptomycin lost vestibular function, but this was no handicap. No patient had gross hearing loss. Among 17 patients who received intrathecal streptomycin, increased vomiting, fever, and irritability occurred shortly after each injection so that less frequent injections were used in several. One patient developed signs of transverse myelitis at the site of intrathecal injection. Another had generalized convulsions when intrathecal strepomycin was given daily but not when the drug was given every other day. Of 26 patients receiving Promizole, 2 showed important toxic reactions. One infant had marked cyanosis with chocolate-colored blood which contained neither methemoglobin nor sulfhemoglobin. The cyanosis disappeared within twelve hours when Promizole was discontinued and ascorbic acid administered intravenously. A second child suddenly developed severe hemolytic anemia with marked cyanosis, respiratory distress, and chocolate-colored blood, approximately ten days after the institution of Promizole and PAS therapy. Recovery was prompt when PAS and Promizole were discontinued. Burgundy-red-colored urine, apparently due to a degradation product of Promizole, was encountered regularly in all patients given this drug. All 3 patients who received neomycin B had toxic nephrosis at autopsy and had had microscopic hematuria and cylindruria, without nitrogen retention, during neomycin therapy. One patient developed sterile abscesses at the site of neomycin injection. In 9 patients tubercle bacilli were isolated six weeks to three hundred and six days after starting therapy; and the bacilli became streptomycin-resistant in only one patient after ninety-six days of treatment. Bacterial resistance to streptomycin did not appear to be a factor in the failure of many cases of tuberculous meningitis.—*Treatment of tuberculous meningitis in children, T. L. Perry, J. Pediat., June, 1952, 40: 687.*—(*M. J. Small*)

Intermittent Streptomycin Therapy.—Streptomycin need not be present continuously in the blood stream to be effective clinically against tubercle bacilli. *In vitro*, tubercle bacilli become incapable of reproduction for some time after exposure for several hours to streptomycin. Concentrations corresponding to those in the blood after an injection of 1 gm. of streptomycin inhibit tubercle bacilli *in vitro* almost completely for sixty-two hours after exposure; lower concentrations are effective for twenty-four to forty-eight hours; higher concentrations do not improve the results. *In vivo* experiments with intermittent administration were performed on guinea pigs inoculated with 0.02 mg. of virulent tubercle bacilli. Eight animals were treated with two daily injections of 10,000 units of streptomycin; 8 others received the same dose every third day; the remaining 8 served as controls. While the latter showed extensive generalized tuberculosis, the therapeutic effect was considerable and practically identical in the other groups. The average weight of lymph nodes in the untreated controls was 4.20 gm. as compared with 0.05 gm. with daily streptomycin and 0.72 gm. with intermittent streptomycin. The corresponding figures for the weight of the spleen were 1.60, 0.86, and 1.08 gm., respectively. A second series of experi-

ments was performed with three groups of guinea pigs treated daily, every other day, and every third day. They were all inoculated with 0.05 mg. of H37Rv and treatment was started two weeks after infection. The average weight of the lymph nodes was 3.61 gm. in the controls, 0.55 gm. with daily streptomycin, 0.69 gm. with streptomycin every other day, 0.67 gm. with streptomycin every third day. Splenic weights were comparable. Similar results were obtained if tuberculosis was evaluated according to the maximal number of visible granulations in those organs. Clinically, no essential difference could be demonstrated in the incidence of favorable results obtained with daily and intermittent streptomycin. It is believed that complete streptomycin sensitivity is essential to obtain maximal benefit from the intermittent regimen. Contrary to these results, *in vitro* experiments with intermittent *p*-aminosalicylic acid seem to indicate that daily administration is superior.—*Évolution légitime de la streptomycinothérapie en tuberculose pulmonaire, E. Bernard & B. Kreis, Presse méd., June, 1952, 60: 825.*—(*V. Leites*)

Streptomycinase.—In an effort to determine possible causes of streptomycin resistance, the possible formation of a streptomycin inactivating substance was investigated. Such a substance, reported as having been isolated from strains of *P. pyocyaneus* and an enterococcus in patients being treated with streptomycin, exhibited enzymatic properties. As evidence for such an enzyme, a decrease in the concentration of streptomycin was looked for in a culture of streptomycin resistant tubercle bacilli which was compared with an exactly similar but uninoculated culture tube. Using a dilution method and an agar cup assay, it was not possible to demonstrate any inactivation of the streptomycin during the growth of streptomycin-resistant bacilli. *Streptomycinase, E. Espersen, Acta path. et microbiol. Scandinav., 1951, 29: 277.*—(*H. G. Turner*)

Detection of Streptomycin Resistance.—A method for determining streptomycin resistance utilized tubes with Lowenstein-Jensen medium and varying concentrations of streptomycin. The pathologic specimen containing the bacilli to be tested was implanted directly on these media. Potassium tellurite was added; it blackens the colonies and makes them visible as soon as they develop. Thus, streptomycin sensitivity or resistance can be determined after ten days.—*Titrage direct de la streptomycino-résistance du bacille de Koch par la technique "au tellurite", A. Meyer & R. Galland, Presse méd., June, 1952, 60: 841.*—(*V. Leites*)

Determination of Bacterial Resistance.—Solid media and direct titration are best for determining bacterial resistance. At the Paris Pasteur Institute, 4,000 titrations have been made and indicate that the antibiotic should not be heated but added to the surface of the medium after coagulation. Flat Legroux tubes present a surface of 50 sq. cm.; the valuation is referred to the square centimeter instead of to the cubic centimeter. Water-soluble and insoluble antibiotics are equally well tested with this method. The macroscopic results are precise and available after two to four weeks. Lowenstein-Jensen medium with glycerin or Dubos medium with agar, with or without egg yolk, are preferred. With this method, the normal sensitivity to streptomycin is 1γ per sq. cm.; to *p*-aminosalicylic acid, 0.1γ per sq. cm.; to amithiozone, 1γ per sq. cm.; to 1358 F, 50γ; to neomycin, 100γ; and to viomycin, 10γ per sq. cm.—*Méthode directe d'étude de la résistance du "Mycobacterium tuberculosis" aux antibiotiques, appréciation qualitative et quantitative de cette résistance, P. J. Caletsas, Presse méd., December, 1951, 59: 1772.*—(*V. Leites*)

Treatment of Skin Tuberculosis.—Between 1941 and 1951, 230 patients with skin tuberculosis received various forms of treatment. In lupus, electro-coagulation gave durable results in 9 per cent of the cases, improvement with frequent relapses in 46 per cent, and failure with rapid exacerbations and considerable mutilation in 45 per cent. Large doses

of vitamin D_2 and calcium produced permanent results without esthetic impairment in 33 per cent of the cases; 33 per cent had apparent arrest with subsequent relapses; 33 per cent were partial and complete failures. Streptomycin with or without *p*-aminosalicylic acid (PAS) gave 30 per cent stable cures, 40 per cent considerable improvements, and 30 per cent failures. Antimicrobial therapy associated or alternated with vitamin D_2 and calcium produced 55 per cent complete cures, 22 per cent marked improvements, and 23 per cent partial and complete failures necessitating electro-coagulation. In tuberculosis verrucosa, vitamin D_2 and calcium produced cure in 16 per cent, improvement in 50 per cent, and failure in 36 per cent; streptomycin was followed by cure in 70 per cent of the cases and by improvement in 30 per cent; PAS gave 62 per cent cures and 38 per cent improvements. The association of streptomycin and PAS followed by vitamin D_2 and calcium gave 79 per cent cures, 14 per cent improvements, and 7 per cent failures. In scrofuloderma, the results were, with vitamin D_2 and calcium: 14 per cent cures, 50 per cent improvements, and 30 per cent failures; with streptomycin: 66 per cent cures, 17 per cent improvements, and 17 per cent failures; with PAS: 70 per cent cures, 20 per cent improvements, and 10 per cent failures; with streptomycin and PAS in association or alternation with vitamin D_2 and calcium: 75 per cent cures, 15 per cent ameliorations, and 10 per cent failures.—*Les traitements actuels de la tuberculose cutanée (d'après 230 cas observés de 1941 à 1951), intérêt de l'alternance des antibiotiques du bacille de Koch et de fortes doses de vitamin D_2*, *C. Huriez, Presse méd., November 21, 1951, 59: 1538.* (*V. Leites*)

Intravenous PAS.—A stable solution of *p*-aminosalicylic acid (PAS) containing 15 gm. of the drug in 500 cc. can be given in daily infusions, each lasting two or three hours, for thirty to sixty days if meticulous care is used to avoid side-effects. Venous sclerosis was observed in 17 per cent of cases after 40 infusions. Febrile reactions were not uncommon but treatment was continued. Manifestations of shock were rare. Gastrointestinal disturbances were exceptional. Favorable results occurred after two to four weeks of treatment; thereafter improvement was usually slight. Of the 45 patients treated, 10 per cent showed no improvement; 30 per cent had excellent immediate results clinically, as well as roentgenographically, with closure of cavities confirmed by serial tomographies. No prolonged follow up is available yet. Intravenous PAS gave moderately good results in 60 per cent of cases without, however, resolving the therapeutic problem. These patients became better candidates for subsequent collapse therapy. Routine use of intravenous PAS is recommended as the initial treatment for cavitary tuberculosis. *Le PAS intraveineux dans le traitement de la tuberculose pulmonaire commune (perfusions discontinues), J. Paraf, P. Zivy, J. Bary, J. Desbordes, & M. Paraf, Presse méd., January 5, 1952, 59: 3.*—(*V. Leites*)

Synergistic Effect of Antibiotics.—The combined effects of streptomycin, sodium *p*-aminosalicylic acid (PAS), viomycin, and neomycin were studied *in vitro* using 4 strains of tubercle bacilli: H37Rv, streptomycin-resistant H37Rv, Brévannes strain, and streptomycin-resistant Brévannes. The antibiotics were used on Löwenstein-Jensen medium in the following 11 combinations: (*1*) two by two in 6 combinations; (*2*) three by three in 4 combinations; (*3*) all 4 together. The most favorable combination was streptomycin and sodium PAS which showed "reinforced synergism"; with one-half of the usual bacteriostatic concentration, a considerably stronger inhibitory effect was produced than with one-half of the usual bacterial concentration of streptomycin, PAS, or viomycin alone. The next best combinations showing "reinforced synergism" were streptomycin-viomycin and PAS-viomycin. Contrary to expectation, none of the triple combinations gave the same favorable results. The combination of one-twelfth of the bacteriostatic concentration of each of the 3 antibiotics produced

definitely weaker bacteriostasis than one-fourth that of each antibiotic used alone. The combination of all 4 antibiotics produced markedly inferior bacteriostasis when compared with the effect produced by each antibiotic alone in an equivalent concentration. The combination of one-twelfth of the bacteriostatic concentration of the 4 antibiotics hardly influenced bacterial growth. It is concluded that below a certain level, probably one-eighth or one-sixth of the usual bacteriostatic concentration, the antibiotic has an insignificant effect. Clinically, the combination of numerous antibiotics is not superior to the judiciously chosen combination of 2 of them.—*L'action synergique in vitro sur Mycobacterium tuberculosis de streptomycine–P.A.S.–viomycine–néomycine dans 11 types d'association. P. J. Coletsos, Rev. de la tubere., 1951, 15: 957.*—(*V. Leites*)

Sulfone and Streptomycin. Twenty-two patients with pulmonary tuberculosis were treated with sulfone and streptomycin. Because 3 of 6 patients on 200 mg. of sulfone daily developed a severe hemolytic anemia, the dosage was reduced to 50 mg. daily. In spite of iron administration throughout, there was an average drop of 10 per cent in the hemoglobin concentration in the 22 patients. Because of the rapid development of resistant strains, the trial was stopped after 22 cases. The therapeutic results of this combination of drugs was not encouraging.—*Sulphone and streptomycin in pulmonary tuberculosis, P. W. Edwards, A. C. Penman, & L. J. Culbill, Brit. M. J., June 7, 1952, No. 4770: 1224.*—(*E. A. Riley*)

LABORATORY STUDIES

Phagocytosis of Tubercle Bacilli. The chemotactic sensitivity of guinea pig leukocytes is diminished or abolished by phagocytosis of tubercle bacilli, as shown by studying chemotaxis of starch granules from potatoes. This inhibition of chemotaxis occurs after the absorption of living or dead, virulent or avirulent bacilli and is proportional to the degree of phagocytosis. The inhibition is associated at first with persistent pseudopodic activity; later, this activity is lost; and, finally, the cytoplasma and the nucleus become altered, leading more or less rapidly to the death of the cell. The lipopolysaccharide antigen extracted by N. Choucroun exerts an inhibitory effect similar to that of virulent tubercle bacilli. The specific properties already established for this substance suggest that it is, at least partly, responsible for the toxic action exerted on leukocytes by the phagocytosis of tubercle bacilli. A blockage of cellular enzymatic systems may explain this toxic action (Author's summary).—*Influence exercée par la phagocytose de bacilles de Koch vivants ou tués et par une fraction lipopolysaccharidique isolée de ces bacilles, sur les phénomènes de migration leucocytaire in vitro, N. Choucroun, A. Delaunay, S. Bazin, & R. Robinneaux, Ann. Inst. Pasteur, June, 1951, 80: 619.*—(*V. Leites*)

Lipid Fraction of Tubercle Bacilli. Certain anionic detergents and surface active substances can extract acid- and alcohol-fast lipid fractions from the peripheral layer of tubercle bacilli. The time required to obtain a certain percentage of cyanophile bacilli was in proportion to their lipid content; it was very long for adult bacilli rich in lipids, shorter for bacilli of attenuated virulence, even shorter for other acid-fast bacilli. BCG ranged between virulent and avirulent bacilli. The "resistance" toward extraction of these lipids depended on the age of the bacilli; it was very weak in young and old strains and strong in the adult phase. In virulent strains, these phases of lability due to youth and aging were short. In these virulent organisms, lipids were numerous and bore a strong electrical charge. Lipids were synthesized from immediately after division until the phase of aging, which was short and ended in the death of the bacillus. In other acid-fast bacilli, these lipids were looser and less adherent; they were synthesized during a rather short period of the adult phase.—*Sur la teneur en "complexe lipidique périphérique" des bacilles acido alcoolo résistants: Notion de cycle vital lipidique de ces germes,*

J. Neshamkes & E. Fournier, Ann. Inst. Pasteur, June, 1952, 82: 713.—(V. Leites)

Growth of Tubercle Bacilli on Egg Fractions.—Egg yolk is a good nutrient for mammalian tubercle bacilli while egg white is a poor nutrient. In the present study, egg yolk was crudely fractionated and the nutrient value of the fractions determined. Acetone, alcohol, and chloroform extracts of yolk were each mixed with egg white in the proportion originally present in the whole egg. These extracts added little to the nutrient properties of the white for growing tubercle bacilli. The residue of yolk remaining after these extractions supported growth about as well as did yolk when added to egg white. Water residues from coagulated yolk and the extracts studied did not support growth satisfactorily. Acid or alkaline hydrolysis of egg yolk, not only destroyed its nutrient properties, but formed deleterious substances which, when added to egg white, completely retarded the growth of mammalian tubercle bacilli.—*The growth of tubercle bacilli on fractions of egg, H. J. Corper & A. Chan, Am. J. Clin. Path., February, 1952, 22: 93.—(J. S. Woolley)*

Cortisone and Tuberculin Allergy.—Guinea pigs injected with 0.09 mg. of *M. tuberculosis*, strain H37Rv, and treated with 5 mg. of cortisone daily showed no inhibition of tuberculin sensitivity and no delay in its development as compared with the controls. There was, however, a slight diminution in the intensity of tuberculin reactions. In a second series of experiments, guinea pigs with experimental tuberculosis received larger doses of cortisone (20 mg. daily) eleven weeks after inoculation. After twelve days of treatment the cutaneous response to 5 mg., 1 mg., and 0.1 mg. of tuberculin was present but was slightly less intense than that obtained before cortisone administration. In order to obtain maximal concentrations of cortisone locally, mixtures of cortisone and tuberculin were injected intradermally into infected guinea pigs and into human volunteers. In the latter, the marked inflammatory reactions, several centimeters in diameter, were identical following tuberculin with saline or tuberculin with cortisone. The control reaction with cortisone alone was always limited to a minimal papule which was just perceptible to palpation. The febrile reaction to subcutaneous tuberculin in animals with experimental tuberculosis was not modified by cortisone administration before or during the tuberculin injection. Animals subjected to tuberculin shock died after the same time interval, with or without cortisone. No exacerbation of tuberculosis was observed in 4 guinea pigs injected with 0.9 mg. of *M. tuberculosis* H37Rv and treated for thirty-nine or fifty days with 5 mg. of cortisone; the course and extent of lesions was comparable in 10 untreated controls.—*Action de la cortisone sur l'allergie tuberculeuse, E. Bernard & B. Kreis, Rev. de la tubere., 1951, 15: 802.—(V. Leites)*

Aerosol Detergent for Viscid Secretions.—In an experimental study, animals were exposed to aerosols of Triton A-20 in concentrations ranging from 0.1 to 50 per cent. The aerosol was generated in a De Vilbiss No. 40 nebulizer for eight hours a day for six consecutive days. The animals were then sacrificed at weekly intervals after exposure, and the tracheobronchial tree and lungs examined grossly and microscopically. No toxic effects were noted. Such aerosols have been used to liquefy viscid bronchopulmonary secretions in patients with a variety of pulmonary diseases. The therapy is safe and more effective than steam or other humidifying procedures.—*A nontoxic detergent for aerosol use in dissolving viscid bronchopulmonary secretions, J. B. Miller & E. H. Boger, J. Pediat., June, 1952, 40: 767.—(M. J. Small)*

Pulmonary Capillary Pressure.—Experimental study of the lesser circulation confirms earlier observations on pulmonary capillary pressure by showing that: (*1*) When a catheter is properly impacted into a peripheral pulmonary artery, the pulmonary capillary pressure is essentially constant except for minor oscillations at the onset and end of ventricular systole. These do not interfere with measurements of the pulmonary capillary pressure.

(*2*) At the end of systole, the capillary pressure usually exceeds that in the left atrium by only 1.5 to 3.7 mm. of mercury; the differences range between 0 and 7 mm. (*3*) When the left atrial pressure is altered experimentally, pulmonary capillary pressure shows corresponding changes. (*4*) Pulmonary capillary pressure is not affected by experimental changes in the pulmonary or aortic pressure even when these are extreme, indicating that pressure is not transmitted to the catheter tip by precapillary pulmonary or bronchial arterial anastomoses. On the other hand, phasic variations in the records of capillary pressure ought to be evaluated carefully with regard to the origin and significance of the pressure waves since: (*a*) Curves displaying phasic variations similar to those attributed to retrograde transmission of left atrial pressure can be recorded from normal dogs. (*b*) The instantaneous pressure measured from such catheter tracings greatly exceeds that in the left atrium, and the contour and time relations of the waves from these two compartments differ. (*c*) Changes in the phasic catheter pressure pulses under experimental conditions follow the trends of pulmonary arterial rather than left atrial pressure. (*d*) Hemodynamic relations therefore indicate that such phasic variations are produced in normal dogs by leakage of pressure around the catheter to its tip. Withdrawal of oxygenated blood from a catheter by suction may not guarantee that there is no such leak. In estimating pulmonary capillary pressure, the only reliable catheter curves are those devoid of phasic changes.—*Interrelations of pulmonary arterial, 'capillary' and left atrial pressures under experimental conditions, J. L. Ankeney, Am. J. Physiol., April 1, 1952, **169:** 40.*—(*G. C. Leiner*)

Artificial Ischemia of the Lung.—To determine how long the lung tissue of a dog remains viable, after occlusion of the entire blood supply, 29 dogs were studied. The pulmonary artery and pulmonary veins were dissected free and occluded by umbilical cord tape. The remainder of the pulmonary hilum, which included the bronchus and bronchial artery, was obstructed in a similar manner. After a period of ischemia, the tapes were released and the lung was re-expanded by positive pressure. In 2 animals, ischemia of the lung was produced for ninety minutes. The ischemic lung, just before and immediately after circulation was re-established and twenty-four hours later could not be distinguished either by gross or by microscopic examination from the control lung. Ischemia was produced for thirty to three hundred and sixty minutes in 24 animals. At autopsy, seven to thirty-four days later, there were no characteristic differences between the ischemic lung and the control lung. An incision made into the ischemic lung showed normal wound healing fourteen days later. In a few animals, there appeared to be a significant drop in the arterial oxygen saturation after temporary ischemia of the lung. Ischemia of the lung for as long as six hours caused astonishingly little morphologic damage. This suggests that this method may be of value in the production of a bloodless field for certain types of pulmonary surgery, in lung transplantation, and may influence techniques for the maintenance of extracorporeal circulation.—*Ischemia of the lung, B. Blades, E. J. Beattie, Jr., R. P. Hill, & R. Thistlethwaite, Ann. Surg., July, 1952, **136:** 56.*—(*M. J. Small*)

Postnatal Pulmonary Blood Volume.—The changes in pulmonary blood volume per unit weight of lung have been determined in guinea pigs at intervals ranging from five minutes to seven hours after birth. This has been done by labeling the blood of fetuses with radioiron and then comparing the radioactivity of lung tissue between breathing and nonbreathing litter mates. The iron labeling was accomplished by the intraperitoneal administration of ferrous sulfate to the pregnant mothers ten to fourteen days before term. Rapid freezing of the newborn made possible the sampling of a lung tissue without lung collapse or blood loss. The results revealed that the lungs at birth contain a considerable amount of blood. After five minutes of breathing the increase in pulmonary blood volume was approximately 24 per cent

and after seven hours the increase averaged 85 per cent (Author's summary).—*Early postnatal changes in pulmonary blood volume of the guinea pig, N. B. Everett, Am. J. Physiol., April 1, 1952, 169: 34.*—(*G. C. Leiner*)

PUBLIC HEALTH AND EPIDEMIOLOGY

Tuberculosis and Mental Hospitals.—The seriousness of the problem of tuberculosis in mental institutions is illustrated by the fact that, although 2.8 per cent of deaths in England and Wales due to tuberculosis occur in mental hospitals, the inmates of mental institutions constitute only 0.35 per cent of the entire population. The over-all incidence of tuberculin reactors in a large mental hospital in Yorkshire was 89.9 per cent of women and 96.5 per cent of men. The majority of patients were more than 40 years old. The highest percentage of reactors was among those patients with the longest residence in the hospital. A roentgenographic survey of 1,199 male patients revealed 54 unsuspected cases of tuberculosis, among whom 25 had either cavitation or a positive sputum. Patients in mental hospitals with active undiagnosed pulmonary tuberculosis represent one of the principal foci of tuberculosis infection remaining in Great Britain.—*Tuberculosis in mental hospitals, B. T. Mann, Brit. M. J., June 7, 1952, No. 4770: 1228.*—(*E. A. Riley*)

Primary and Reinfection Tuberculosis in Peru.—Among 50 autopsied Peruvian adults who died from tuberculosis, 9 (18 per cent) died as a result of primary infection; 28 (56 per cent), as a result of reinfection. In 13 cases (26 per cent) no conclusion was reached, as the lesions were not characteristic of either type. In the primary group, Indians and persons newly arrived from the country or small villages predominated. Pathologically, the only significant difference between the two types was the presence of caseated enlarged satellite lymph nodes. Among Indians the infection tended to spread by the lymphatic route. This was unusual among white or half-breed individuals. The data suggest that in Peru not all patients are infected with tuberculosis in childhood.—*Patología de la infección tuberculosa primaria en el adulto, J. Campos Rey de Castro, Rev. tubere., January-December, 1951, 11: 1.*—(*A. A. Moll*)

Healed Tuberculosis.—After a number of patients previously considered as clinically healed had returned to the author's hospital, he attempted to contact 168 "healed" patients. Of these, 35 could not be found. In all, 71 patients (42.3 per cent) have been readmitted to the hospital for further treatment of their tuberculosis. According to the patients, recurrence was caused by insufficient care at home.—*The problem of recurrence in treated and clinically healed cases of pulmonary tuberculosis (Yugoslav), T. Drinkovic, Tuberkuloza, December, 1951, 3: 395.*—(*J. Hawsky*)

BCG Vaccination in Malta.—In a BCG vaccination campaign in Malta in 1950, 48,319 individuals between the ages of one and eighteen were tuberculin tested by the epinephrine-Pirquet technique. The results of 42,986 tests are known, and 36,320 persons were given BCG. Complications of the test were rare. Approximately 85 per cent of the individuals tested were nonreactors. During the first fifteen years of life the incidence of positive reactors was almost identical in both sexes; from the ages of 15 to 20 there was a higher incidence of positive reactors among the men. There were more cases of active tuberculosis in this age group among men than women, but the former had a significantly lower mortality. BCG vaccination was carried out by the Wallgren intradermal injection technique. Complications were few. There were 11 cases of the Koch phenomenon as an accelerated abnormal reaction at the site of vaccination which occurred in those persons already infected with tubercle bacilli. The 23 cases of discharging ulcers tended to appear between the thirtieth and fifty-third days after vaccination; in 2, the fever and constitutional symptoms responded to *p*-aminosalicylic acid. The 54 cases of glandular enlargement usually developed two to four months after vaccination and proceeded to suppuration one to three months later. All

these glandular reactions developed on the side which was vaccinated, and none was accompanied by mediastinal adenopathy. Material aspirated from these abscesses contained tubercle bacilli. To test the conversion rate, 2,421 unselected vaccinated individuals were tested and 1,975 (98.95 per cent) gave a positive reaction. Of the 446 nonreactors, 8 eventually became positive after three to six months; prompt revaccination may be unjustified. Following vaccination one case of erythema nodosum and 17 cases of phlyctenular conjunctivitis occurred. This would seem to confirm the view that phlyctens are an allergic manifestation of tuberculous infection. Plans have been devised for the future follow-up of all the cases vaccinated.—*Mass B.C.G. vaccination in Malta, V. Zammit-Tabona Brit. M. J., April 19, 1952, No. 4736: 837.*—(*E. A. Riley*)

Accelerated Reaction to BCG.—Accelerated reactions after BCG vaccination occur in persons with positive tuberculin reactions. During the BCG campaign in Timor, Indonesia, 30,000 persons were vaccinated without previous tuberculin testing. The frozen-dried vaccine of the Paris Pasteur Institute was used. A group of 371 persons received a Pirquet test and BCG vaccination simultaneously and the reactions were read after sixty-two hours. In this group, 78 persons had an accelerated BCG reaction and a positive Pirquet test; 262 had a normal BCG reaction and a negative Pirquet test; 29 had an accelerated reaction and a negative Pirquet but a positive Mantoux test; 2 persons had a normal BCG reaction and a positive Pirquet although they may not have received a full dose of vaccine because of marked cutaneous atrophy. A second group of 214 persons had accelerated reactions but they were not tuberculin-tested in order to avoid error. The accelerated reactions in this group had the same course as those in the group which had received simultaneous tuberculin tests. The accelerated reaction to BCG began with a red infiltration around the site of infection a few hours after vaccination; this reached its maximum, with a diameter up to 35 mm. sixty-two hours later. Sometimes many small papules appeared and, on the fifth day, became confluent. Although some contained an opaque gray fluid, suppuration was never present. On the sixth day, the papules dried up and the infiltration practically disappeared. The characteristic infiltration appears in nonallergic persons during the third or fourth week but occurs in the persons with accelerated reaction between the eighth and tenth days. From then on, the BCG reaction is similar in the two groups. No complications occurred in the 214 persons with an accelerated reaction, which suggests that BCG vaccination can safely be performed without previous tuberculin testing. Roentgenographic examination of persons with an accelerated reaction is recommended.—*A propos de quelques cas de reactions locales dites "accélérées" consécutives à la vaccination par voie intradermique avec du BCG congelé desséché, V. M. Oppers, Ann. Inst. Pasteur, July, 1951, 81: 43.*—(*V. Leites*)

BCG in Exposed Children.—BCG vaccine may best be evaluated in persons actually exposed to tuberculous infection. This study included 446 infants living in an infected or suspected environment and vaccinated at birth with 0.09 gm. of BCG. The exposure lasted from one month to more than one year. Examinations were made in 317 children (71.1 per cent) at the end of the first year, in 199 (44.6 per cent) at the end of the second year, and in 276 (61.9 per cent) at the end of the seventh year; 106 children (23.8 per cent) were examined all three times. During the observations, 17 cases of tuberculosis were detected, 6 in infants under one year of age, 8 in children between one and two years, and 3 in children over two years. Of the 17 patients, 8 were cured, 4 died, and 5 could not be followed. Even including these 5 cases among the dead, the death rate would be only approximately 2 per cent. The disease rate was less than 1 per cent.—*Vacinação B.C.G. em crianças com contágio tuberculoso, A. MacDowell filho, Rev. brasil. tubarc., May-June, 1952, 20: 165.*—(*A. A. Moll*)

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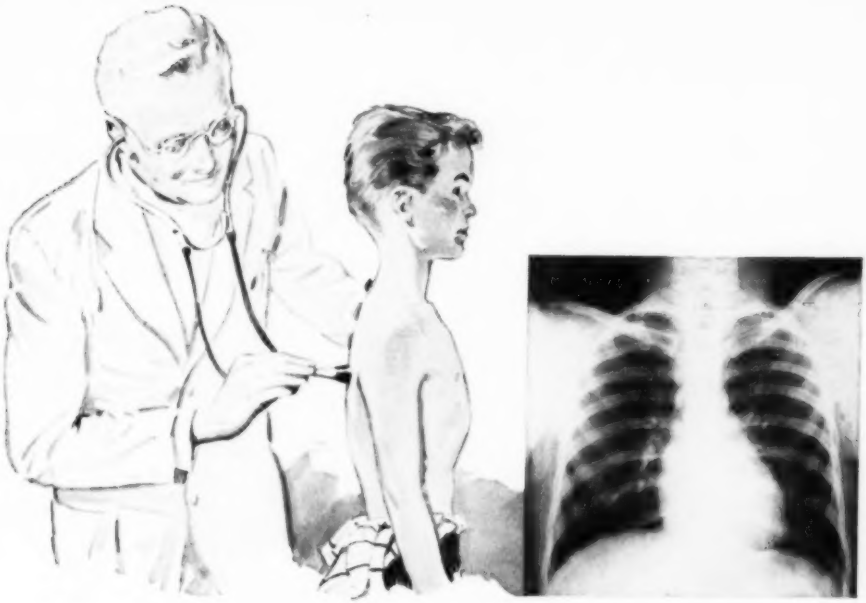

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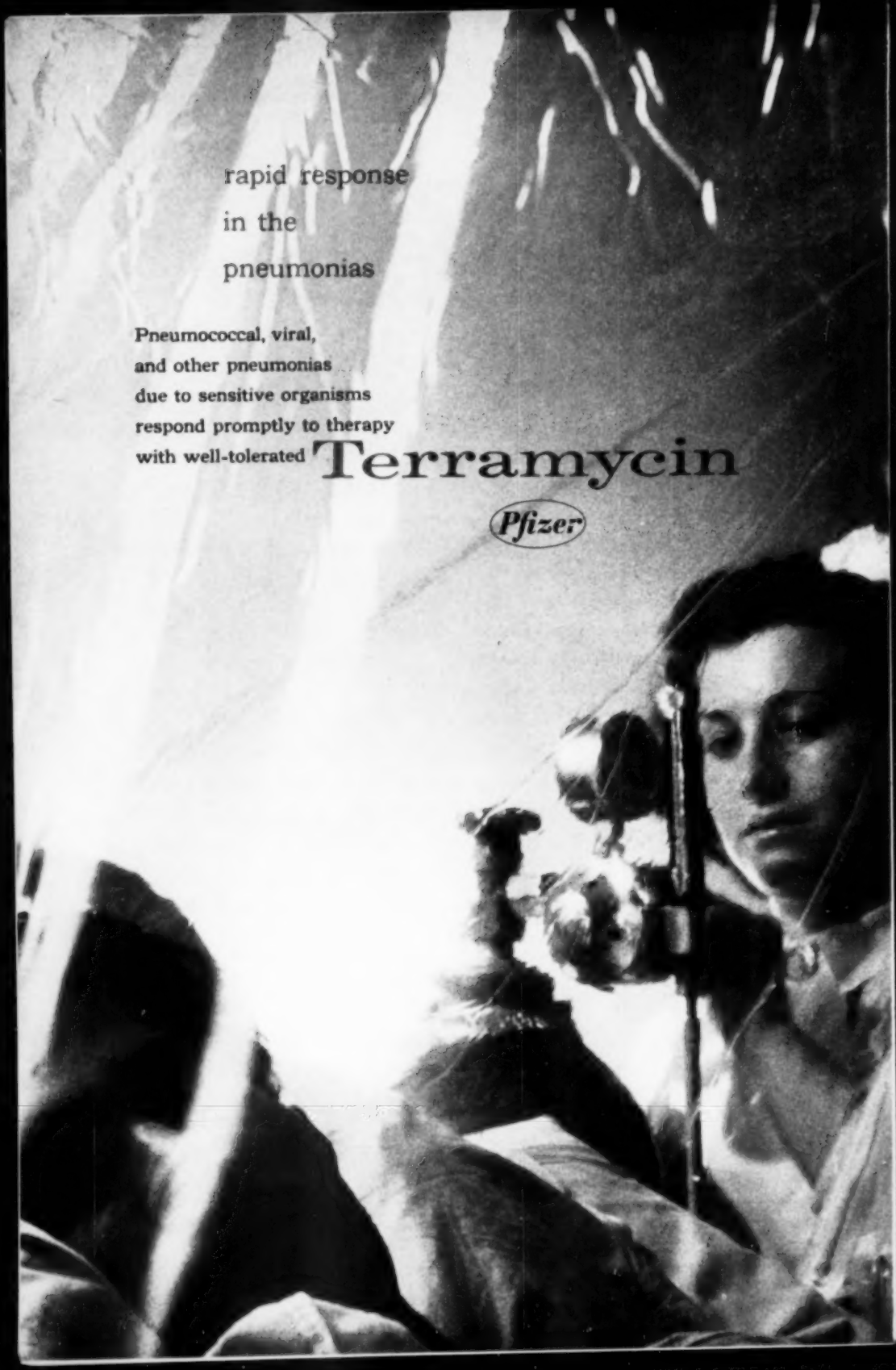
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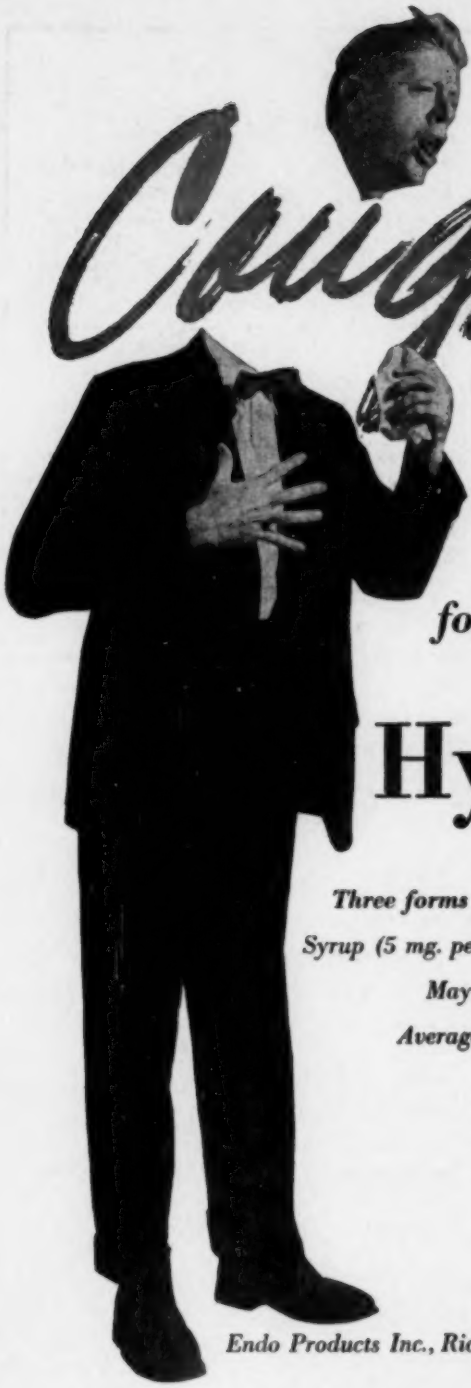

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